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Pat nt Search

Fulltext

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TITLE (ENGLISH): INHIBITION OF p38 KINASE ACTIVITY USING SUBSTITUTED HETEROCYCLIC UREAS
TITLE (FRENCH): INHIBITION DE L'ACTIVITE DE P38 KINASE AU MOYEN D'UREES HETEROCYCLIQUES SUBSTITUEES
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ABSTRACT (ENGLISH):
This invention relates to the use of a group of aryl ureas in treating cytokine mediated diseases, other than cancer and proteolytic enzyme mediated diseases, other than cancer, and pharmaceutical compositions for use in such therapy.

ABSTRACT (FRENCH):
L'invention a trait a l'utilisation d'un groupe d'aryle urees pour traiter des maladies, autres que le cancer, induites par des cytokines, et des maladies, autres que le cancer, induites par des enzymes proteolytiques; et a des compositions utiles pour ce type de therapie.

DESCRIPTION:
io Inhibition of p38 Kinase Activity Using Substituted Heterocyclic Ureas
Field of the Invention
This invention relates to the use of a group of aryl ureas in treating cytokine mediated
diseases and proteolytic enzyme mediated diseases, and pharmaceutical compositions
for use in such therapy.

Backeround of the Invention
Two classes of effector molecules which are critical for the progression of rheumatoid
arthritis are pro-inflammatory cytokines and tissue degrading proteases. Recently, a
family of kinases was described which is instrumental in controlling the transcription
and translation of the structural genes coding for these effector molecules.

The mitogen-activated protein (MM) kinase family is made up of a series of structurally related proline-directed serine/threonine kinases which are activated either
by growth factors (such as EGF) and phorbol esters (ERK), or by IL-1, TNF(X or
stress (p38, JNK). The kinases are responsible for the activation of a wide variety of transcription factors and proteins involved in transcriptional control of
cytokine production. A pair of novel protein kinases involved in the regulation of
cytokine synthesis was recently described by a group from SmithKline Beecham (Lee
et al. Nature 1994, 372, 739). These enzymes were isolated based on their affinity to
bond to a class of compounds, named CSAIDSs (cytokine suppressive anti-inflammatory drugs) by SKB. The CSAIDs. bicyclic pyridinyl imidazoles, have been
shown to have cytokine inhibitory activity both in vitro and in vivo. The isolated
enzymes, CSBP-1 and -2 (CSAID binding protein 1 and 2) have been cloned and expressed. A murine homologue for CSBP-2, p38, has also been reported (Han et al.

Science 1994, 265, 808).

Early studies suggested that CSAIDs function by interfering with m-RNA translational events during cytokine biosynthesis. Inhibition of p38 has been shown
to inhibit both cytokine production (eg., TNFa, IL-1, IL-6, IL-8) and proteolytic
enzyme production (eg., MMP-1, NRVIP-3) in vitro and/or in vivo.

Clinical studies have linked TNF(x production and/or signaling to a number of diseases including rheumatoid arthritis (Maini. J Royal Coll. Physicians London
1996, 30, 344). In addition, excessive levels of TNFa have been implicated in a wide
io variety of inflammatory and/or immunomodulatory diseases, including acute rheumatic fever (Yegin et al. Lancet 1997, 349, 170), bone resorption (Pacifici et al.

J. Clin. Endocrinol. Metabol. 1997, 82, 29), postmenopausal osteoperosis (Pacifici et
al. J Bone Mineral Res. 1996, 11, 1043), sepsis (Blackwell et al. Br. J Anaesth.

1996, 77, 1 1 0), grain negative sepsis (Debets et al. Prog. Clin. Biol. Res. 1989, 308,
463), septic shock (Tracey et al. Nature 1987, 330, 662; Girardin et al. New England
J Med. 1988, 319, 397), endotoxic shock (Beutler et al. Science 1985, 229, 869;
Ashkenasi et al. Proc. Nat'l. Acad. Sci. USA 1991, 88, 10535), toxic shock syndrome,
(Saha et al. J. Immunol. 1996, 15 7, 3 869; Lina et al. FEMS Immunol. Med. Microbiol.

1996, 13, 81), systemic inflammatory response syndrome (Anon. Crit. Care Med.

19929 20] 864), inflammatory bowel diseases (Stokkers et al. J. Inflamm. 1995-6, 47,
97) including Crohn's disease (van Deventer et al. Aliment. Pharmacol. Therapeu.

1996, 10 (Suppl. 2), 107; van Dullemen et al. Gastroenterology 1995, 109, 129) and
ulcerative colitis (Masuda et al. J Clin. Lab. Immunol. 1995, 46, 111), Jarisch-
Herxheimer reactions (Fekade et al. New England J Med 1996, 335, 31 1), asthma
(Amrani et al. Rev. Malad. Respir. 1996, 13, 539), adult respiratory distress syndrome
(Roten et al. Am. Rev. Respir. Dis. 1991, 143, 590; Suter et al. Am. Rev. Respir. Dis.

19929 145, 1016), acute pulmonary fibrotic diseases (Pan et al. Pathol. Int. 1996, 46,
91), pulmonary sarcoidosis (Ishioka et al. Sarcoidosis Vasculitis Diffuse Lung Dis.

1996, 13, 139), allergic respiratory diseases (Casale et al. Am. J Respir. Cell Mol.

3o Biol. 1996, 152 35), silicosis (Gossart et al. J Immunol. 1996, 156, 1540; Vanhee et
al. Eur. Respir. J 1995, 8, 834), coal worker's pneumoconiosis (Borm et al. Am. Rev.

Respir. Dis. 1988, 138, 1589), alveolar injury (Horinouchi et al. Am. J Respir. Cell
Mol. Biol. 1996, 14, 1044), hepatic failure (Gantner et al. J Pharmacol. Exp. Therap.

Transplant. Proc. 1990, 22, 1924), lung allograft rejection (Grossman et al. Immunol.

Allergy Clin. N. Am. 1989, 9, 153) including chronic lung allograft rejection
(obliterative bronchitis; LoCicero et al. J Thorac. Cardiovasc. Surg. 1990, 99, 1059),
as well as complications due to total hip replacement (Cirino et al. Life

Sci. 1996, 59,
86). TNFoc has also been linked to infectious diseases (review: Beutler et al. Crit.

Care Med. 1993, 21, 5423; Degre. Biotherapy 1996, 8, 219) including tuberculosis
(Rook et al. Med. Malad Infect. 1996, 26] 904), Helicobacter pylori infection during
peptic ulcer disease (Beales et al. Gastroenterology 1997, 112, 136), Chaga's disease
resulting from Trypanosorna cruzi infection (Chandrasekar et al. Biochern. Biophys.

Res. Commun. 1996, 223, 365), effects of Shiga-like toxin resulting from E. coli
infection (Harel et al. J Clin. Invest. 1992, 56, 40), the effects of enterotoxin A
resulting from Staphylococcus infection (Fischer et al. J 1mmunol. 1990, 144, 4663),
meningococcal infection (Waage et al. Lancet 1987, 355; Ossege et al. J Neurolog.

Sci. 1996, 144, 1), and infections from Borrelia burgdorferi (Brandt et al. Infect.

Immunol. 1990, 58, 983), Treponerna pallidum (Chamberlin et al. Infect. Immunol.

1989, 57, 2872), cytomegalovirus (CMV; Geist et al. Am. J Respir. Cell Mol. Biol.

1997, 16, 31), influenza virus (Beutler et al. Clin. Res. 1986, 34, 491 a), Sendai virus
(Goldfield et al. Proc. Nat'l. Acad Sci. USA 1989, 87, 1490), Theiler's
encephalomyelitis virus (Sierra et al. Immunology 1993, 78, 399), and the human
immunodeficiency virus (HIV; Poli. Proc. Nat'l. Acad. Sci. USA 19909 87] 782;
Vyakaram et al. AIDS 1990, 4, 2 1; Badley et al. J Exp. Med. 1997, 185, 55).

Because inhibition of p38 leads to inhibition of TNF(x production, p38 inhibitors will
be useful in treatment of the above listed diseases.

A number of diseases are thought to be mediated by excess or undesired matrix-
destroying metalloprotease (M]M11) activity or by an imbalance in the ratio of the
MMPs to the tissue inhibitors of metalloproteinases (THAps). These include
osteoarthritis (Woessner et al. J Biol. Chem. 1984, 259, 3633), rheumatoid arthritis
(Mullins et al. Biochim. Biophys. Acta 1983, 695, 117; Woolley et al. Arthritis
Rheum. 1977, 20, 1231; Gravallese et al. Arthritis Rheum. 1991, 34, 1076), septic
arthritis (Williams et al. Arthritis Rheum. 1990, 33, 533), tumor metastasis (Reich et
al. Cancer Res. 1988, 48, 3307; Matrisian et al. Proc. Naft Acad Sci., USA 1986, 83,
), periodontal diseases (Overall et al. J Periodontal Res. 1987, 22, 81), corneal

ulceration (Bums et al. Invest. OpthalmoL Vis. Sci. 1989, 30, 1569), proteinuria (Baricos et al. Biochem. J 1988, 254, 609), coronary thrombosis from atherosclerotic plaque rupture (Henney et al. Proc. Nat'l. Acad Sci., USA 1991, 88, 8154), aneurysmal aortic disease (Vine et al. Clin. Sci. 1991, 81, 233), birth control (Woessner et al. Steroids 1989, 54, 491), dystrophobic epidermolysis bullosa (Kronberger et al. J Invest. DermatoL 1982, 79, 208), degenerative cartilage loss following traumatic joint injury, osteopenias mediated by Nimp activity, tempero mandibular joint disease, and demyelating diseases of the nervous system (Chantry et al. J Neurochem. 1988, 50, 688).

Because inhibition of p38 leads to inhibition of NUAP production, p38 inhibitors will be useful in treatment of the above listed diseases.

Inhibitors of p38 are active in animal models of TNFa production, including a muirne lipopolysaccharide (LPS) model of TNFcc production. Inhibitors of p38 are active in a number of standard animal models of inflammatory diseases, including carrageenan-induced edema in the rat paw, arachadonic acid-induced edema in the rat paw, arachadonic acid-induced peritonitis in the mouse, fetal rat long bone resorption, murine type II collagen-induced arthritis, and Fruend's adjuvant-induced arthritis in the rat. Thus, inhibitors of p38 will be useful in treating diseases mediated by one or more of the above-mentioned cytokines and/or proteolytic enzymes.

The need for new therapies is especially important in the case of arthritic diseases.

The primary disabling effect of osteoarthritis, rheumatoid arthritis and septic arthritis is the progressive loss of articular cartilage and thereby normal joint function. No marketed pharmaceutical agent is able to prevent or slow this cartilage loss, although nonsteroidal antiinflammatory drugs (NSAIDs) have been given to control pain and swelling. Theendresultofthesediseasesistotallossofjoint:ftmctionwhichisonly treatable by joint replacement surgery. P38 inhibitors will halt or reverse the progression of cartilage loss and obviate or delay surgical intervention.

Several patents have appeared claiming polyarylimidazoles and/or compounds containing polyarylimidazoles as inhibitors of p38 (for example, Lee et al. WO 95/07922; Adams et al. WO 95/02591; Adams et al. WO 95/13067; Adams et al. WO 95/31451). It has been reported that arylimidazoles complex to the ferric form of cytochrome P450,an, (Harris et al. MoL Eng. 1995, 5, 143, and references therein), causing concern that these compounds may display structure-related toxicity

(Howard-Martin et al. ToxicoL PathoL 1987, 15, 369). Therefore, there remains a
need for improved p38 inhibitors.

Summary of the Invention
This invention provides compounds, generally described as aryl 'ureas, including both
aryl and heteroaryl analogues, which inhibit p38 mediated events and thus inhibit the
production of cytokines (such as TNFa, IL-1 and IL-8) and proteolytic enzymes (such
as MMP- I and MMP-3). The invention also provides a method of treating a cytokine
mediated disease state in humans or mammals, wherein the cytokine is one whose
production is affected by p38. Examples of such cytokines include, but are not
limited to TNFa, IL-1 and IL The invention also provides a method of treating a
proteate mediated disease state in humans or mammals, wherein the protease is one
whose production is affected by p38. Examples of such proteases include, but are not
limited to collagenase (MW-1) and stromelysin (MMP-3).

Accordingly, these compounds are useful therapeutic agents for such acute and
chronic inflammatory and/or immunomodulatory diseases as rheumatoid arthritis,
osteoarthritis, septic arthritis, rheumatic fever, bone resorption, postmenopausal
osteoperosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock
syndrome, systemic inflammatory response syndrome, inflammatory bowel diseases
including Crohn's disease and ulcerative colitis, Jarisch-Herxheimer reactions,
asthma, adult respiratory distress syndrome, acute pulmonary fibrotic diseases,
pulmonary sarcoidosis, allergic respiratory diseases, silicosis, coal worker's
pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute
inflammation, severe alcoholic hepatitis, malaria including Plasmodiurn falciparum
malaria and cerebral malaria, non-insulin-dependent diabetes mellitus (NIDDM),
congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's
Accordingly, the present invention is directed to a method for the treatment of
2o diseases mediated by one or more cytokine or proteolytic enzyme produced and/or
activated by a p38 mediated process, comprising administering a compound of
formula I
0
1 1
A-TN.H-C-NH-B
wherein B is generally an unsubstituted or substituted, up to tricyclic, aryl or
heteroaryl moiety with up to 30 carbon atoms with at least one 5 or 6 member
aromatic structure containing 0-4 members of the group consisting of

nitrogen,
oxygen and sulfur. A is a heteroaryl moiety discussed in more detail below.

The aryl and heteroaryl moiety of B may contain separate cyclic structures and can
include a combination of aryl, heteroaryl and cycloalkyl structures. The substituents
for these aryl and heteroaryl moieties can vary widely and include halogen, hydrogen,
hydrosulfide, cyano, nitro, amines and various carbon-based moieties, including those
which contain one or more Of Sulfur. nitrogen, oxygen and/or halogen and are
discussed more particularly below.

Suitable aryl and heteroaryl moieties for B of formula I include, but are not limited to
aromatic ring structures containing 4-30 carbon atoms and 1-3 rings, at least one of
which is a 5-6 member aromatic ring. One or more of these rings may have 1-4
carbon atoms replaced by oxygen, nitrogen and/or sulfur atoms.

Examples of suitable aromatic ring structures include phenyl, pyridinyl, naphthyl,
pyrimidinyl, benzothiazolyl, quinoline, isoquinoline, phthalimidinyl and combinations
thereof, such as diphenyl ether (phenyloxyphenyl), diphenyl thioether
(phenylthiophenyl), diphenyl amine (phenylaminophenyl), phenylpyridinyl ether
(pyridinyloxyphenyl), pyridinylmethylphenyl, phenylpyridinyl thioether
(pyridinylthiophenyl), phenylbenzothiazolyl ether (benzothiazolyloxyphenyl),
phenylbenzothiazolyl thioether (benzothiazolylthiophenyl), phenylpyrimidinyl ether,
phenylquinoline thioether, phenylnaphthyl ether, pyridinylnapthyl ether,
pyridinylnaphthyl thioether, and phenylphthalimidylmethyl.

Examples of suitable heteroaryl groups include, but are not limited to, 5-12 carbon-
2o atom aromatic rings or ring systems containing 1-3 rings, at least one of which is
aromatic, in which one or more, e.g., 1-4 carbon atoms in one or more of the rings can
be replaced by oxygen, nitrogen or sulfur atoms. Each ring typically has 3-7 atoms.

For example, B can be 2- or 3-ftiryl, 2- or 3-thienyl, 2- or 4-triazinyl, 1-, 2- or 3-
pyrrolyl, I-, 2-, 4- or 5-imidazolyl, I-, 3-t 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4-
or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-,
5- or 6-pyrimidinyl, 1,2,3-triazol-1-, or yl, 1,2,4-triazol-1-, or yl, 1- or 5-
tetrazolyl, 1,2,3-oxadiazol or yl, 1,2,4-oxadiazol or yl, 1,3,4-thiadiazol
or yl, 1,2,4-oxadiazol or yl, 1,3,4-thiadiazol or yl, 1,3,4-thiadiazol
or yl, 1,2,3-thiadiazol or yl, 2-, 3-,, 4-, 5- or 6-2H-thiopyranyl, 2-, 3- or 4-
3o 4H-thiopyranyl, 3- or 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or 7-benzoftiryl, 2-, 3-,
4-, 5-, 6- or 7-benzothienyl, 1-, 2-] 3-] 4-] 5-9 6- or 7-indolyl, 1-, 2-, 4- or 5-
benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-9 6- or

7-benzoxazolyl,
3-, 4-, 5- 6- or 7-benzisoxazolyl, 1-, 3-, 4-9 5-, 6- or 7-benzothiazolyl,
2-, 4-,] 5-9 6- or
7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benz-1,3-oxadiazolyl, 2-9 3-] 4-] 5-]
6-] 7- or 8-
quinolinyl, I-, 3-, 4-, 5-, 6-, 7-, 8- isoquinolinyl, 1-, 2-, 3-, 4- or
9-carbazolyl, 1-, 2-,
3-] 4-9 5-5 6-] 7-1, 8- or 9-acridinyl, or 2-, 4-, 5-5 6-, 7- or
8-quinazolinyl, or additionally
optionally substituted phenyl, 2- or 3-thienyl, 1,3,4-thiadiazolyl, 3-pyrryl,
3-pyrazolyl,
2-thiazolyl or 5-thiazolyl, etc. For example, B can be 4-methyl-phenyl,
5-methyl
thienyl, 4-methyl thienyl, 1-methyl pyrryl, 1-methyl pyrazolyl, 5-methyl
thiazolyl or 5-methyl-1,2,4-thiadiazol yl.

Suitable alkyl groups and alkyl portions of groups, e.g., alkoxy, etc.
throughout
include methyl, ethyl, propyl, butyl, etc., including all straight-chain and
branched
io isomers such as isopropyl, isobutyl, sec-butyl, tert-butyl, etc.

Suitable aryl groups include, for example, phenyl and 1- and 2-naphthyl.

Suitable cycloalkyl groups include cyclopropyl, cyclobutyl, cyclohexyl, etc.
The term
i5 cycloalkyl, as used herein, refers to cyclic structures with or without
alkyl
substituents such that, for example, C4 cycloalkyl includes methyl
substituted
cyclopropyl groups as well as cyclobutyl. groups. The term cycloalkyl also
includes
saturated heterocyclic groups.

Suitable halogens include F, Cl, Br, and/or I, from one to persubstitution
(i.e., all H
atoms on the group are replaced by halogen atom), being possible, mixed
substitution
of halogen atom types also being possible on a given moiety.

As indicated above, these ring systems can be unsubstituted or substituted by
substituents such as halogen up to per-halosubstitution. Other suitable
substituents for
the moieties of B include alkyl, alkoxy, carboxy, cycloalkyl, aryl,
heteroaryl, cyano,
hydroxy and arnine. These other substituents, generally referred to as X and
X
herein, include -CN, -CO2R-', -C(O)NRR, -C(O)R, -NO2. -OR, -SR, -NRR,
.NR'C(O)OR, -NRC(O)R, CI-CIO alkYl, C2-Clo alkenylq CI-Clo alkoxy, C3-CIO
cycloalkyl, C6-CI4 aryl, C7-C24 alkarYl. C3-CI3 heteroaryl, C4-C23
alkheteroaryl,
substituted CI-Clo alkyl, substituted C2-Clo alkenyl, substituted CI-Clo
alkoxy,
substituted C3-CIO cycloalkyl, substituted C4-C23 alkheteroaryl and -Y-Ar.

Where a substituent, X or X', is a substituted group, it is preferably
substituted by one
or more substituents independently selected from the group consisting of
--CN,
-CO2R', -C(O)R, -C(O)NR-'R. -OR, -SR, -NRR . -NO2. -NR5C(O)W',

The moieties R5 and R5' are preferably independently selected from HI CI-Clo alkyl,
C.)- 3-C10 cycloalkyl, C6-C14 aryl, C3-C13 heteroaryl, C7-C24 alkaryl, C4-C23 alkheteroaryl, up to per-halosubstituted CI-Clo alkyl, Up to per-halosubstituted C,)-
10 alkenyl, up to per-halosubstituted C3-C10 cycloalkyl, up to per-halosubstituted C6-
C14 aryl and up to per-halosubstituted C3-C13 heteroaryl.

The bridging group Y is preferably , -S-, -N(R 5)_1 -(CH2)-m, _C(O)_] io -NR5C(O)NRR. -NR'C(O)-, -C(O)NR', -CH(011)-] -(CH2)mO-, -(CH2)mS-, -(CHDmN(R)_] -O(CH2)m-9 _CHXa, _CXa 2-, -S-(CH2).- and -N(R5)(CH2)m-, where ra
= 1-3, and X' is halogen.

The moiety Ar is preferably a 5-10 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally
substituted by Z,,,, wherein n1 is 0 to 3.

Each Z substituent is preferably independently selected from the group consisting of
-CN, -CO2R5, =09 _C(O)NR5R5', _C(O)_NR5. -NO29 -OR', -SR 5] _i]R5R5', _NR5C(O)ORI', -C(O)R 5, _NR5C(O)R, -SO2R 51 -SO2NR5R5', C1-C10 alkyl, C1-C10 alkoxy, C3-C10 cycloalkyl, C6-C14 arYl, C3-C13 heteroaryl, C7-C24 alkaryl, C4-C23
alkheteroaryl, substituted CI-Clo alkyl, substituted C3-C10 cycloalkyl, substituted C7-
C24 alkaryl and substituted C4-C23 alkheteroaryl. If Z is a substituted group, it is
substituted by the one or more substituents independently selected from the group
consisting of -CN, -CO2R, -C(O)NRR, =O, -OR'] -SR5. -NO2] _NR5RI -NR'C(O)R. -NWC(O)OR, CI-Clo alkyl, CI-Clo alkoxy, C3-C10 cycloalkyl, C-CIO heteroaryl, C6-C14 aryl, C4-C24 alkheteroaryl and C7-C24 alkaryl.

The aryl and heteroaryl moieties of B of Formula I are preferably selected from the
group consisting of
0 0
R5 R5
N N
and
which are unsubstituted or substituted by halogen, up to per-halosubstitution. X is as
defined above and n = 0
The aryl and heteroaryl moieties of B are more preferably of the formula IL
X
n
-Q- (Y-Qt-Zn1
wherein Y is selected from the group consisting of , -S-, -CH2-, SCH2-, -CH2S-9
-CH(OH)-, -C(O)-, -CXa2, -CXaH-, -CH20- and -OCH2- and X' is halogen.

Q is a six member aromatic structure containing 0-2 nitrogen, substituted or unsubstituted by halogen, up to per-halosubstitution and Q1 is a mono- or bicyclic
aromatic structure of 3 to 10 carbon atoms and 0-4 members of the group consisting

of N, 0 and S, unsubstituted or unsubstituted by halogen up to per-halosubstitution.

X, Z, n and n1 are as defined above and s = 0 or 1.

In preferred embodiments, Q is phenyl or pyridinyl, substituted or unsubstituted by
halogen, up to per-halosubstitution and Q1 is selected from the group consisting of
lo The heteroaryl moiety A of formula I is preferably selected from the group consisting
of-
R RI Rs R I
N],,Rc N Rc Nj']'s
I I
N v
N
RI I I I
R RI R R
I RI
W]Q 0'] S N N]N,,N
I =
N J\ L N
N s
I R RI\
R R
0 s
N and
s
Rb Rb
The substituent R1 preferably is selected from the group consisting of halogen, C3-CIO
alkyl, CI-C13 heteroaryl, C6-C14 aryl, C7-C24 alkylaryl, C3-CIO cycloalkyl, up to per-
halosubstituted CI-Clo alkyl and up to per-halosubstituted C3-Clo cycloalkyl, up to
per-halosubstituted CI-C13 hetero, up to per-halosubstituted C6-C13 aryl and up to per-
halosubstituted C7-C24 alkaryl.

2o The substituent R2 is preferably selected from the group consisting of H. -C(O)W2
-CO2R!, C(O)NR3W'g CI-CIO alkYl. C3-CIO cycloalkyl, C7-C24 alkarYl, C4-C23
alkheteroaryl, substituted Cj-CjO alkyl, substituted C3-CIO cycloalkyl, substituted C7-
C24 alkaryl and substituted C4-C23 alkheteroaryl. Where R2 is a substituted group, it is
preferably substituted by one or more substituents independently selected from the
group consisting of -CN, - C02R], -C(O)-NR3R3'. -NO2, -OR]] -SW, and halogen up
to per-halosubstitution.

R3 and W' are preferably independently selected from the group consisting of H,
-OR]2 -SR4. -Nlft]', -C(O)R4. -CO2R4. -CMWW'] CI-CIO alkYl, C3-CIO cycloalkyl,
C6-C14 arYl. C3-CI3 heteroaryl, C7-C24 alkaryl, C4-C23 alkheteroaryl, up to per-
halosubstituted CI-CIO alkyl, up to per-halosubstituted C3-CIO cycloalkyl, up

to per-
halosubstituted C6-CI4 aryl and up to per-halosubstituted C3-CI3 heteroaryl.

R] and R]'are preferably independently selected from the group consisting of H, Cj-
CIO alkyl, C3-CIO cycloalkyl, C6-CI4 arYl, C3-CI3 heteroaryl; C7-C24 alkaryl, C4-C23
io alkheteroaryl, up to per-halosubstituted CI-CIO alkyl, up to per-halosubstituted C3-CIO
cycloalkyl, up to per-halosubstituted C6-CI4 aryl and up to per-halosubstituted C3-CI3
heteroaryl.

Ra is preferably CI-CIO alkyl, C3-CIO cycloalkyl, up to per-halosubstituted CI-CIO alkyl
and. up to per-halosubstituted C3-CIO cycloalkyl.

R] is preferably hydrogen or halogen.

R' is hydrogen, halogen, CI-CIO alkyl, up to per-halosubstituted CI-Clo alkyl or
combines with R1 and the ring carbon atoms to which RI and R' are bound to form a
5- or 6-membered cycloalkyl, aryl or heteroaryl ring with 0-2 members selected from
0, N and S.

Preferred pyrazolyl ureas include those wherein B is 2 dichlorophenyl or of the
formula II above, wherein Q is phenyl, Q1 is phenyl or pyridinyl, Y ix , -S-, -CH2
or -SCH2, X is CF3, Z is OH, C1 or -NHC(O)-CpH2p+1, wherein p = 2-4, s = 0 or 1, n
0 or 1 and n1 = 0 or 1. Particular preferred pyrazolyl ureas include.

N-(3-tert-Butyl pyrazolyl)-N]-(4-(2,3-dichlorophenyl)urea;
N-(3-tert-Butyl pyrazolyl)-N!-(3-(4-pyridinyl)thiophenyl)urea;
N-(3-tert-Butyl pyrazolyl)-N!-(4-(4-pyridinyl)methylphenyl)urea;
N-(3-tert-Butyl pyrazolyl)-N]-(4-(4-pyridinyl)oxyphenyl)urea;
N-(3-tert-Butyl pyrazolyl)-N]-(4-(4-pyridinyl)thiophenyl)urea;
N-(3-tert-Butyl pyrazolyl)-N!-(4-(4-pyridinyl)methylphenyl)urea;
N-(I-Methyl tert-butyl pyrazolyl)-N]-(2,3-dichlorophenyl)urea;
10 E SI A 41Au!p!i]dio lAuaqd si i,) lIXuotld
do 'Ho ST Z JD SI X 6ZHD-
si uioioiqm 'OAoqv II vinuLIOJ QIP JO SI a U!DJQIItA SR= 1XIOZEXOST-E65
Pouojolcl
TOM (lAuoqcUxo(lAp!jAd-17)-tp)-,N-(IAIOzEJAd-g-lf4nq-i-lai-E)-N
puuto.m OE
tram (IKuolqd(on
. plAppAd
-t)-t,jX,qjouio.ionUL tu
!.go.jn (1,Kuzqdon Amou,
troin (lXuoqdou ZUL]
tam (lAuoqdon
p 9z
lAqiou,-I)-N
!ro.mQXuQiqd
-Ixqlotu(lXui
.P.

!,oo.in-(jXuoijdo-iojtjolp
oz
t7zjn(IXuz,qdo.ioIqoi
.P
-o.iolqot
.P
!uoxn(lAuoqdo.iolq-3!p-EIZ)-,,V-(IXlozujAd-g-lAlnq-;.Ia;-E-(IsqIOAxO.IPXH-Z)-
0-N
!uo.in(lXuoqd 5 i
-o-iollqoi
.P
!,uo.in(lXuoqd
-(oi P.

.qjIAT4joTuQAui
!vomQAuoqdAxoQAui ui]
.p. d-
f-oo.inQXuoqd-QAtjjotuo.ionUL
.4) oi
.P.

tain(lAuoqdou
.41(lXui
.P.

!vo.in(IXuolqdoi QAui E-IAIIIQW- I)-IV
RI P.

!po.mQAuoqdop
(IAuzqd
-lAuoq,iEoouiumlSinqosi-tp)-t7)-,N-(IAlozrjAd-g-lf4nq-;-iai-E-lAqioW-I)-m 9
to.mQAuz,qdoi
RI
0809Z/86S[I/JL3d I II U/66 OM
-OCpH2p+1, wherein p = 2-6, or -C(O).NH-CH3, S = 1, n = 0 or 1, and n is 0 or
1.

Particular preferred 5 isoxazolyl ureas include.

N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-hydroxyphenyl)oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-isopropoxyphenyl)oxyphenyl)urea;
N--(5-tert-Butyl isoxazolyl)-N-(4-(4-isobutoxyphenyl)oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-pentyloxyphenyl)oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-methylaininocarbonylphenyl)-
oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N]-(3-(4-pyridinyl)thiophenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N]-(3-(4-pyridinyl)oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)thiophenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)methylphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-pyridinyl)thio (trifluoromethyl)-
phenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N]-(3-(3-methyl pyridinyl)thiophenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N'-(3-(3-methyl pyridinyl)oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N]-(4-(3-methyl pyridinyl)oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N]-(4-(3-methyl pyridinyl)thiophenyl)urea;
N-(5-tert-butyl isoxazolyl)-N-(4-(4-(2-methylcarbamoyl)pyridyl)-
oxyphenyl) urea;
N-(5-tert-butyl isoxazolyl)-N'-(3-(4-(2-methylcarbamoyl)pyridyl)-
oxyphenyl) urea;

N-(5-tert-butyl isoxazolyl)-N'-(4-(4-(2-carbainoyl)pyridyl)oxyphenyl) urea;
N-(5-tert-butyl isoxazolyl)-N-(3-(4-(2-carbamoyl)pyridyl)oxyphenyl) urea;
N-(5-tert-butyl isoxazolyl)-N]-(3-((4-pyridyl)fluoromethyl)phenyl) urea;
and
N-(5-tert-butyl isoxazolyl)-N]-(3-((4-pyridyl)oxomethyl)phenyl) urea.

Preferred 3,5-isoxazolyl ureas include those wherein B is 2,3-dichlorophenyl or of
the formula 11 above, wherein Q is phenyl, Q1 is phenyl, pyridinyl or benzothiazolyl,
urea;
N-(3-tert-butyl isoxazolyl)-N]-(4-(4-pyridyl)methylphenyl) urea; and
N-(3-tert-butyl isoxazolyl)-N]-(4-(4-methoxyphenyl)aminophenyl) urea.

Preferred thienyl ureas, furyl ureas and thiadiazolyl ureas include those wherein B is
2,3-dichlorophenyl of the fonnula H above, wherein Q is phenyl, Q1 is phenyl or
pyridinyl, Y is , -S- or -CH2-, Z = CH3, OH, Cl, -O-C2H4 or -O-C3H7, s = 0 or 1,
n = 0 and n1 = 0 or 1. Preferred thienyl ureas include.

N-(2-Bromo tert-butyl thienyl)-N]-(4-methylphenyl)urea;
N-(5-tert-Butyl thienyl)-N]-(2,3-dichlorophenyl)urea;
N-(5-tert-Butyl thienyl)-N]-(4-(4-hydroxyphenyl)oxyphenyl)urea;
N-(5-tert-Butyl thienyl)-N'-(4-(4-ethoxyphenyl)oxyphenyl)urea;
N-(5-tert-Butyl thienyl)-N'-(4-(4-isopropoxyphenyl)oxyphenyl)urea;
'lXdo.id-u JO Z(EHD)HDZHD-O-'z(EHD)N
-(O)D- 'lXlnq-u ' lf4uod-u ljf4nq-j (o)D-HN- 'lAuoqd-zHD sl 9-d UloJQqAk
9]1. 0 HN HN
N
u
(q ol
Ho -0 N N 0
11 H I
0 N
ne-1
:o,ulnuuoj oiqljo spunodiuoo Qpnloui Allpogloods oiotu pule QAoqv paqposop
I Elnuuoj IviouoS jo adoos 0q) UT
.ql!tA OM q3F
.4M 01 S01-0101 091V UOT AUT olqL
Po
.P.

pucto.m(l,]uoiqdon
U(lAui
.p!lAd-tr)-t7)-,N-(jAuon
. p-C-jf4nq-jaaj-g)-N
!roxn(lAuoqciAxo(lAu!ppAd-tp)-tr)-,N-(IAuon
. p-C-jAjng-ma;-g)-N
!uo.m(lAuQqdAxo(l,]uippAd-E)-t7)-,N-(IAuon
0809V86Sfl/JLDd LI I II ZC/66 OM
C)
Rl
N 0
1 1 1-
u N -C N 0 CH3
H H
wherein Rl is-CH2-t-butyl;
d)

t-Bu
N 0
1 11
In H-C-N
R
wherein R2 is -CH2-CF3, -c2H,4-OH, -CH2-(3-HOC6H4), -CH2C(O)NH3.

-cH2C(O)OC2H5, -C2H4CN, or
CH
0
1 1
O-CANH
Cl cl
t-Bu
N 0 0
H 11 H 11
VN N-C-N---] C-O-C4H9
CH3
f)
t-Bu
0
SL-]: 11
NH-C-NHC]-O-C]-OCH(CH 3)2
g)
Br
N 0
11 11
s- NH-C-NH-] CH3
and
h)
CH(CH3)2
CH3
N
I 0
11
NH-C-NH
Preferred compounds also include the following thiadiazoles and thiophenes.

N-(5 -tert-butyl (1 -thia-3,4-diazolyl))-N]-(4-(4-pyridyl)oxyphenyl) urea;
N-(5-tert-butyl (I-thia-3,4-diazolyl))-N]-(3-(4-pyridyl)thiophenyl) urea;
AJoj!qn
p osruq 71ntwo ui paq osop spunoduioo
SEd ssossodqoi
.qm I L j]i
JO ULIOJ OA1 DE All-cm doio onuomi polialosi Aur sossudiumuo um Aui luosaid
oqjL
.1 .1 RUO .

aqj U! pollqs ouO 01 MAAOU)j llom On soinimui opolUO0101SUIP pug OUOLUOIJUBUO
JO um ndos JO spoqjoW -SUU0j OA1 DE All-colido pur onuomi ui 1swo omplotp
Re .1
weo put suoqno o!4ounmAsu ssassod I vinuuoj JO spunodwoo mp JO ioqtunu V oz
ouo-L-oopun[0-j7-g]ojoAwqtzm
P
-861 pur (Naa) ouo-g-uou[0-C--V]oloAmqvzm -g'l '(03ava)
P
ouujoo[Z-Z-Z]ojwqez-ai -tr'l '(dVW(j) out Um
.ppAdoui jAqjoun -NN 'oulppXd
P P
IOUTUMIAxotjopAoi -ATW louiumlAqlai -ArN loui lAqjoL Te

um JO um 141P.Iod Io gz
P P
um uoloiduio4guTsLmosoipsuqonssuoi oummounuukmuiolunbptm'tuniuoumm
Re it,
poinijisps Di tuam put Di ildip Sui njout 4sos-eq onm&o JO silts ppr SE 110M
Re Re . P
SE 'U011ro U.Mruounur QTjj 6(z -egio z UD I z 2w 6 3) SUOTIVO qpro oullmllu
M.10 -gm
ill o)suoi oouilmUtftu luoosllrsst)lqons'sosuqomBiouijosllrsp!o-e])pnloui
+4 .110 . TO
silts olquidoom Allmilnooleumqd 6uoij!ppv ul -ppr Di opurTu put 'plor
wjQorlxUQqd oz
4ppe oilAoijvs Ippe oiozuoq 'ppv walrui Ippr oLmumj 4ppr oluloons 'plot
oilexo
'plov Di oul 'plor oL
.4p 6plou oLmlml Ippr oiltnu 4ppu Di oovoionu]n 4ppe 01 ODE 'P!3v
omoqdlns 'plou oruoqdlnsoueqlztu 1ppv ouoqdsoqd'plo-c o]mqdlns 1ppE
wT.UoiqoipAq
4ppe ouolqooipAq SE qons 'splov oungio pur onmi?.ioui JO silts 3isuq opnjoui
put
w oqi ui pQllqs asoill ol umou)l llom On silts o1qvidooov AllminoovuLmqd
Qlqul!nS -I gi
rlnuuoj JO silts olquidooor XllumjnoovuLmqd ol poloom 0SIE St UO1jU3AU1
TUOsaid Qqj
P
TOM (lXuoqd/ixo(lXuoqd,]xodoidosi-i7)-.V)-,N-(IXuan]4
put tom (lXuoqdXxo(lAuoqdAxoqlo-tv)-i7)-, N-(IAuoi
tom (lAuzqdAxo(lXuoqcfAxoqloui-i7)-t7)-,,V-(IKuou
01
to.in
tom QAuoqdoiolT4m -E'Z)-,N-(lAuoi
.P
tain (lAuoqdlAqlow(lAppAd-i7)-t7)-,N-(IAuou 44
nq-p9j-g)-N
!ro.m (lAuoqdoi
.qjQAppXd-t7)-tp)-,N-(lAuai
.qj-E-jfqnq-maj-g)-N
toin (lXuoqcUxo(lAppAd-t7)-V)-,N-(IAuou 44
!-eojn
(lAuoqd,]xo(lXuoqdlAqlou.i-t7)-E)-,N-((IXlozuip-17'E-ioi
toin
(Ixuoqclxxo(lxuzqcuxoqlatu-tF)-E)-,N-((IXlozui -j7IC-tu
.P p-l)-Z-l14nq-ma;-g)-)V
0809V86Sf1/.L3d 0z I II U/66 OM
General Preparative Methods
The compounds of Formula I may be prepared by use of known chemical reactions and procedures, some from starting materials which are commercially available.

Nevertheless, the following general preparative methods are presented to aid one of skill in the art in synthesizing the inhibitors, with more detailed particular examples being presented in the experimental section describing the working examples.

Heterocyclic amines may be synthesized utilizing known methodology (Katritzky, et al. Comprehensive Heterocyclic Chemistry; Permagon Press: Oxford, UK (1984).

March. Advanced Organic Chemistry, 3d Ed.; John Wiley: New York (1985)). For

example, 3-substituted aminoisoxazoles (3) are available by the reaction of hydroxylarnine with an ct-cyanoketone (2), as shown in Scheme I. Cyanoketone 2, in
turn, is available from the reaction of acetamidate ion with an appropriate acyl
derivative, such as an ester, an acid halide, or an acid anhydride. Reaction of an -
cyanoketone with hydrazine (R2=H) or a monosubstituted hydrazine affords the 3-
substituted- or 1,3-disubstituted aminopyrazole (5). Pyrazoles unsubstituted at N-I
(R]=H) may be acylated at N-1, for example using di-tert-butyl dicarbonate, to give
pyrazole 7. Similarly, reaction of nitrile 8 with a-thioacetate ester gives the 5-
substituted amino thiophenecarboxylate (9, Ishizaki et al. JP 6025221).

Decarboxylation of ester 9 may be achieved by protection of the amine, for example
as the tert-butoxy (BOC) carbainate (10), followed by saponification and treatment
with acid. When BOC protection is used, decarboxylation may be accompanied by deprotection. giving the substituted 3-thiopheneammonium salt 11. Alternatively,
ammonium salt 11 may be directly generated through saponification of ester 9 followed by treatment with acid.

CH3CN
R'
1) base
2) H2NOH*HCI
Ri X NH2
3
R1
NHNH2 4
CN N]
R1]NINH2 0
RO)] X
5
2 R1
R H >
K
R1 N NH2
R' HS.,.CO2R 0 R
cl)]=] S 7
CN -]INH2
8 C02R
9
1) OH- 0 0
2) H >])])1]0-]]
0 0
Ir
R' R1
1) OH-
st] 14 2) H+
NH3+ NHBOC
C02R
11 10
Scheme 1. Selected General Methods for Heterocyclic Amine Synthesis
Substituted anilines may be generated using standard methods (March. Advanced

Organic Chemistry, 3d Ed.; John Wiley: New York (1985). Larock. Comprehensive Organic Transformations; VCH Publishers: New York (1989)). As shown in Scheme II, aryl amines are commonly synthesized by reduction of nitroaryls using a metal
catalyst, such as Ni, Pd, or Pt, and H2 or a hydride transfer agent, such as formate,
cyclohexadiene, or a borohydride (Rylander. Hydrogenation Methods; Academic io Press: London, UK (1985)). Nitroaryls may also be directly reduced using a strong
hydride source, such as LiAlH4 (Seyden-Penne. Reductions by the Alumino- and Borohydrides in Organic Synthesis; VCH Publishers: New York (1991)), or using a
zero valent metal, such as Fe, Sn or Ca, often in acidic media. Many methods exist
H2 / catalyst
(eg. Ni, Pd, Pt)
ArNO2 [H- %sm. ArNH2
(eg. Fe, Sn, Ca)
Scheme 11 Reduction of Nitroaryls to Aryl Amines
Nitroaryls are commonly formed by electrophilic aromatic nitration using HN03, or
an alternative N02+ source. Nitroaryls may be further elaborated prior to reduction.

Thus, nitroaryls substituted with
HN03
Ar-H ON- ArNO2
io potential leaving groups (eg. F, Cl, Br, etc.) may undergo substitution reactions on
treatment with nucleophiles, such as thiolate (exemplified in Scheme III) or phenoxide. Nitroaryls may also undergo Ullman-type coupling reactions (Scheme
02N ArSH
R F
base
12 02N
S-Ar
R:::D-
02N Br-Ar 13
SH
CuO / base
14
Scheme III Selected Nucleophilic Aromatic Substitution using Nitroaryls
As shown in Scheme IV, urea formation may involve reaction of a heteroaryl isocyanate (17) with an aryl amine (16). The heteroaryl isocyanate may be synthesized from a heteroaryl amine by treatment with phosgene or a phosgene equivalent, such as trichloromethyl chloroformate (diphosgene), bis(trichloromethyl)
carbonate (triphosgene), or NN'-carbonyldiimidazole (CDI). The isocyanate may also be derived from a heterocyclic carboxylic acid derivative, such as an ester, an
acid halide or an anhydride by a Curtius-type rearrangement. Thus, reaction of acid
derivative 21 with an azide source, followed by rearrangement affords the isocyanate.

The corresponding carboxylic acid (22) may also be subjected to Curtius-type rearrangements using diphenylphosphoryl azide (DPPA) or a similar reagent. A urea
may also be generated from the reaction of an aryl isocyanate (20) with a heterocyclic amine.

Het-NH2 16 H2N-Ar 19
COC12 COC12
H2N-Ar 0 Het-NH2
Het-NCO)P. Het-,)] Ar oW - OCN-Ar
N N'
17 H H 20
18
N3 PPA N3 PPA
0 0 0 0
HetAX HeClkOH X-kAr HO)]Ar
22 23 24
io Scheme IV Selected Methods of Urea Formation (Het = heterocycle)
1-Amino heterocyclic carboxylic esters (exemplified with thiophene 9, Scheme V)
may be converted into an isatoic-like anhydride (25) through saponification, followed
by treatment with phosgene or a phosgene equivalent. Reaction of anhydride 25 with
an aryl amine can generate acid 26 which may spontaneously decarboxylate, or may
be isolated. If isolated, decarboxylation of acid 26 may be induced upon heating.

RI
R
1) OH-
S 00
_]_]NH2 2) COC12 NH 25
R02C O
9
H2N-Ar
R
R
0 A 0
S a- N 'K N' Ar 49 S)] Ar
H H N N'
H02C H H
27 _J
26
Scheme V Urea Formation via Isatoic-like Anhydrides
Finally, ureas may be further manipulated using methods familiar to those skilled in
the art.

The invention also includes pharmaceutical compositions including a compound of
this invention as described above, or a pharmaceutically acceptable salt thereof, and a
physiologically acceptable carrier.

io The compounds may be administered orally, topically, parenterally, by inhalation or
spray, sublingually, or rectally or vaginally in dosage unit formulations. The term
'administration by injection' includes intravenous, intramuscular, subcutaneous and
parenteral injections, as well as use of infusion techniques. Dermal administration
may include topical application or transdermal administration. One or more

compounds may be present in association with one or more non-toxic pharmaceutically acceptable carriers and if desired other active ingredients.

Compositions intended for oral use may be prepared according to any suitable method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from the group consisting of diluents, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; and binding agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. These compounds may also be prepared in solid, rapidly released form.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions containing the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions may also be used. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene

sorbitan
monooleate. The aqueous suspensions may also contain one or more
preservatives,
for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring
agents, one
or more flavoring agents, and one or more sweetening agents, such as sucrose
or
saccharin.

Dispersible powders and granules suitable for preparation of an aqueous
suspension
by the addition of water provide the active ingredient in admixture with a
dispersing
or wetting agent, suspending agent and one or more preservatives. Suitable
dispersing
or wetting agents and suspending agents are exemplified by those already
mentioned
above. Additional excipients, for example, sweetening, flavoring and coloring
agents,
may also be present.

The compounds may also be in the forrn of non-aqueous liquid formulations,
e.g., oily
io suspensions which may be formulated by suspending the active ingredients
in a
vegetable oil, for example arachis oil, olive oil, sesame oil or peanut oil,
or in a
mineral oil such as liquid paraffin. The oily suspensions may contain a
thickening
agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents
such
as those set forth above, and flavoring agents may be added to provide
palatable oral
preparations. These compositions may be preserved by the addition of an
anti-oxidant
such as ascorbic acid.

Pharmaceutical compositions of the invention may also be in the form of
oil-in-water
emulsions. The oil phase may be a vegetable oil, for example olive oil or
arachis oil,
or a mineral oil, for example liquid paraffin or mixtures of these. Suitable
emulsifying agents may be naturally-occurring gums, for example gum acacia or
gum
tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin,
and
esters or partial esters derived from fatty acids and hexitol anhydrides, for
example
sorbitan monooleate, and condensation products of the said partial esters
with
ethylene oxide, for example polyoxyethylene sorbitan monooleate. The
emulsions
may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example
glycerol,
propylene glycol, sorbitol or sucrose. Such formulations may also contain a
3o demulcent, a preservative and flavoring and coloring agents.

The compounds may also be administered in the form of suppositories for

rectal
administration of the drug. These compositions can be prepared by mixing the drug
with a suitable non-irritating excipient which is solid at ordinary temperatures but
Compounds of the invention may also be administrated transdermally using methods
known to those skilled in the art (see, for example: Chien; Transdermal Controlled
Systemic Medications; Marcel Dekker, Inc.; 1987. Lipp et al. W094/04157
3Mar94). For example, a solution or suspension of a compound of Formula I in a
suitable volatile solvent optionally containing penetration enhancing agents can be
io combined with additional additives known to those skilled in the art, such as matrix
materials and bacteriocides. After sterilization, the resulting mixture can be
formulated following known procedures into dosage fon-ns. In addition, on treatment
with emulsifying agents and water, a solution or suspension of a compound of
Formula I may be formulated into a lotion or salve.

Suitable solvents for processing transdermal delivery systems are known to those
skilled in the art, and include lower alcohols such as ethanol or isopropyl alcohol,
lower ketones such as acetone, lower carboxylic acid esters such as ethyl acetate,
polar ethers such as tetrahydrofuran, lower hydrocarbons such as hexane, cyclohexane
or benzene, or halogenated hydrocarbons such as dichloromethane, chloroform,
trichlorotrifluoroethane, or trichlorofluoroethane. Suitable solvents may also include
mixtures of one or more materials selected from lower alcohols, lower ketones, lower
carboxylic acid esters, polar ethers, lower hydrocarbons, halogenated hydrocarbons.

Suitable penetration enhancing materials for transdermal delivery system are known
to those skilled in the art, and include, for example, monohydroxy or polyhydroxy
alcohols such as ethanol, propylene glycol or benzyl alcohol, saturated or unsaturated
C8-CI8 fatty alcohols such as lauryl alcohol or cetyl alcohol, saturated or unsaturated
C8-CI8 fatty acids such as stearic acid, saturated or unsaturated fatty esters with up to
3o 24 carbons such as methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl isobutyl
tertbutyl or monoglycerin esters of acetic acid, capronic acid, lauric acid, myristinic
acid, stearic acid, or palmitic acid, or diesters of saturated or unsaturated dicarboxylic
acids with a total of up to 24 carbons such as diisopropyl adipate, diisobutyl adipate,
diisopropyl sebacate, diisopropyl maleate, or diisopropyl furnarate. Additional
Suitable binding materials for transdermal delivery systems are known to

those skilled
in the art and include polyacrylates, silicones, polyurethanes, block polymers,
styrenebutadiene coploymers, and natural and synthetic rubbers. Cellulose ethers,
derivatized polyethylenes, and silicates may also be used as matrix components.

Additional additives, such as viscous resins or oils may be added to increase the
viscosity of the matrix.

For all regimens of use disclosed herein for compounds of Formula 1, the daily oral
dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The
daily dosage for administration by injection, including intravenous, intramuscular,
subcutaneous and parenteral injections, and use of infusion techniques will preferably
be from 0.01 to 200 mg/Kg of total body weight. The daily rectal dosage regimen
will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily vaginal
dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The
daily topical dosage regimen will preferably be from 0.1 to 200 mg administered
between one to four times daily. The transdermal concentration will preferably be that
required to maintain a daily dose of from 0.01 to 200 mg/Kg. The daily inhalation
dosage regimen will preferably be from 0.0 I to 1 0 mg/Kg of total body weight.

It will be appreciated by those skilled in the art that the particular method of
administration will depend on a variety of factors, all of which are considered
routinely when administering therapeutics.

It will also be understood, however, that the specific dose level for any given patient
will depend upon a variety of factors, including, the activity of the specific compound
employed, the age of the patient, the body weight of the patient, the general health of
the patient, the gender of the patient, the diet of the patient, time of administration,
route of administration, rate of excretion, drug combinations, and the severity of the
condition undergoing therapy.

It will be further appreciated by one skilled in the art that the optimal course of
treatment, ie, the mode of treatment and the daily number of doses of a compound of
Formulae I or a pharmaceutically acceptable salt thereof given for a defined number
of days, can be ascertained by those skilled in the art using conventional

course of
treatniment tests.

The entire disclosure of all applications, patents and publications cited above and
below are hereby incorporated by reference, including provisional application Attorney Docket No. Bayer I 1 VI, filed December 22, 1997, as SN 08/995,750, and
was converted on December 22, 1998.

The following examples are for illustrative purposes only and are not intended, nor
should they be construed to limit the invention in any way.

EXAMPLES
All reactions were performed in flame-dried or oven-dried glassware under a positive
pressure of dry argon or dry nitrogen, and were stirred magnetically unless otherwise
indicated. Sensitive liquids and solutions were transferred via syringe or cannula, and
introduced into reaction vessels through rubber septa. Unless otherwise stated, the
term 'concentration under reduced pressure' refers to use of a Buchi rotary evaporator
at approximately 15 mmHg.

All temperatures are reported uncorrected in degrees Celsius ff). Unless otherwise
io indicated, all parts and percentages are by weight.

Commercial grade reagents and solvents were used without further purification.

Thin-layer chromatography (TLC) was performed on Whatmang pre-coated glass-backed silica gel 60A F-254 250 gm plates. Visualization of plates was effected by
one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to
iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid
in ethanol followed by heating, (d) immersion of the plate in a cerium sulfate solution
followed by heating, and/or (e) immersion of the plate in an acidic ethanol solution of
2,4-dinitrophenylhydrazine followed by heating. Column chromatography (flash chromatography) was performed using 230-400 mesh EM Science] silica gel.

Melting points (mp) were determined using a Thomas-Hoover melting point apparatus
or a Mettler FP66 automated melting point apparatus and are uncorrected. Fourier
transform intrared spectra were obtained using a Mattson 4020 Galaxy Series spectrophotometer. Proton (H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric GN-Omega 300 (300 MHz) spectrometer with either Me4Si (8 0.00) or residual protonated solvent (CHC13 8 7.26; MeOH 8 3.30;
DMSb 8 2.49) as standard. Carbon (13 Q NMR spectra were measured with a General Electric GN-Omega 300 (75 MHz) spectrometer with solvent (CDC13 5 77.0;

MeOD-d3; 5 49.0; DMSO-d6 8 39.5) as standard. Low resolution mass spectra (MS)
and high resolution mass spectra (HRMS) were either obtained as electron impact (EI)
mass spectra or as fast atom bombardment (FAB) mass spectra. Electron impact mass spectra (El-MS) were obtained with a Hewlett Packard 5989A mass
Elemental analyses were conducted by Robertson Microlit Labs, Madison NJ. All ureas displayed NMR spectra, LRMS and either elemental analysis or HRMS consistant with assigned structures.

List of Abbreviations and Acronyms.

AcOH acetic acid
anh anhydrous
BOC tert-butoxycarbonyl
conc concentrated
3o dec decomposition
DMPU 1,3-dimethyl-3,4,5,6-tetrahydro-2(lH)-pyrimidinone
DMF NN-dimethylformamide
DMSO dimethylsulfoxide
DPPA diphenylphosphoryl azide
MeOH methanol
pet. ether petroleum ether (boiling range 30-60 'C)
THF tetrahydrofuran
TFA trifluoroacetic acid
io Tf trifluoromethanesulfonyl
A* General Methods for Synthesis of Hetrocyclic Arnines
A2. General Synthesis of 5-Amino alkylisoxazoles
0
CN
Step 1. 3-Oxo methylpentanenitrile: A slurry of sodium hydride (60% in mineral
oil; 10.3 g, 258 mmol) in benzene (52 niL) was warmed to 80 'C for 15 min., then a
solution of acetonitrile (13.5 mL, 258 mmol) in benzene (52 mL) was added dropwise
via addition fimnel followed by a solution of ethyl isobutyrate (15 g, 129 minol) in
benzene (52 mL). The reaction mixture was heated overnight, then cooled with an ice
water bath and quenched by addition of 2-propanol (50 mL) followed by water (50
mL) via addition funnel. The organic layer was separated and set aside. EtOAc (100
inL) was added to the aqueous layer and the resulting mixture was acidified to
approximately pH 1 (conc. HCI) with stirring. The resulting aqueous layer was extracted with EtOAc (2 x 100 mL). The organic layers were combined with the original organic layer, dried (MgSO4), and concentrated in vacuo to give the a-
cyanoketone as a yellow oil which was used in the next step without further purification.

N
0 NH2
9z
GS) Clog 6(HZ's Jq) Zlog '(HZ'ZH 6*9=0) V017 '(HZ
'zH 6*9--F'I) Z87 IH6 6s) Ell 2 (9P-0SWG) -dM-H, IC-OfU (Qu-9xQlq %0L/0V0la
%oz) DriL :(%OE 'S g*z) jonpaid pansop otp piojjt7 ol (auuxoq/0zja)
pol-em-41g

SUIA ligualmi gm nsai oiql p
.11 U'u (QU13XOq %0C/3V0la %OL 01 Zu'uxOlq %09/DV019
%0tF tuo-U lu0jp,9B) voij!s JO ptd v q2nojql pojollU sm onppai Qqj pur amssaid oz
POMPO-I WM P0124MMOO Sum ojmx!Tu oqj, -uopovai ololdwoout pomoqs sisspur DrIj, lq3'r m U!
.qM JOUP lq2lLUQAO oim-modiml xnUoi oqj 1-c polroq sm (I 001) H019
QOuRu 6%St7 T 19-0 Oulzu-Tkq 1,KqlQ0urX0-Z PUB (IOUItu c*.vty' 9*g) 1. luodoxo
2? a L4!UQUu
-E-jXqiotui -174tp JO uoi los V :alozuiXd(lXqlaouui;)-Z)-l-li]4nq-lial-E-ouimv-s
.P Rn
ON
zHN N
saj0zvlAdjA3jjv-E-jS3jju- I-ouitaV-S jo uoi viudajd aqj ioj poqlaN junuaf) oEV
LZI (Q0u9Punq'u 10-0 zlzu SW-aVj !(HI 's) VV*9 6(HZ 's) 080-V '(HI 'zH O*L=r 61clos)
ZL'Z IH9 4zH O*L=f 4P) UT P (9P-0SWG) UKM-H, !61]0 (IlDzHD %96/0uOl03'0 01 %9) --d DPIJL !Do 99-E9 du-I :(%OL 'S E& II) MlOs m0110A V sfe 010zox0s' PAIMP 0T.11
pjojju 01 (zlDzHD %06/QuO103P %0 1) voij!s JO pud u qSnojqj paiollu sum pps mollox
Allo Sui Insai aqL -onom uz polaquamw pim 1(tYOSEW) pou
p wom sioXvI mm&o
pouiqiuoo oq.L -2ui ow jnoqjjm (qw 001 x 0 ElDHD Wm PlOv4xa XI0j-u!P0umul
sTtA ojmxiui uoilonj uLmm oql -11o molloX osuop ssol r oonpaid ol sinoq g-Z ioj g
D. og ir pol-niq sTm uoi los molloX SuilInsai oqL -2uLulls oli
Rn qm ojjjj!uourjuodjAlqj0w
-t-oxo-C optuo JO uoT os v olu! pamod s-em uoi los Sui Insai oip pu-e (qm CL) .1ni Rn .1
101M ul QOuItu gtP9 '2 6* 9Z) HGON JO uOllnlOs P100 031 uu 01 POPPE AVAOls MA QOuRu
8trl 'S E*01) ap!jojqoojpAq ouiumjAxoipAH :ajozvxosijSdoidosi-E-omtuV-S *Z dalS
0809V86Sfi/13d I II U/66 OM
A 4. Synthesis of 3-Amino alkylthiophenes-
A4a. Synthesis of 3-Amino alkylthiophenes by Thermal Decarboxylation of Thiophenecarboxylic Acids
NH
0]]o
Step 1. 7-tert-Butyl-2H-thieno[3,2-d]oxazine-2,4(1H)-dione: A mixture of methyl
3-amino tert-butylthiophenecarboxylate (7.5 g, 35.2 mmol) and KOH (5.92 g) in MeOH (24 mL) and water (24 mL) was stirred at 90 'C for 6 h. The reaction mixture
was concentrated under reduced pressure and the residue was dissolved in water (600
mL). Phosgene (20% in toluene, 70 mL) was added dropwise over a 2 h period. The
io resulting mixture was stirred at room temperature overnight and the resulting
precipitate was triturated (acetone) to afford the desired anhydride (5.78 g, 73%): 'H.

NMR (CDC13) 8 1.38 (s, 9H), 2.48 (s, 1H), 6.75 (s, 1H); FAB-MS mlz (rel abundance)
226 ((M+H)+g 100%).

0
N N
HOO H H
Step 2. N-(5-tert-Butyl carboxy thienyl)-N]-(4-(4-pyridinylmethyl)phenyl)-
urea: A solution of 7-tert-butyl-2H-thieno[3,2-d]oxazine-2,4(lH)-dione (0.176
g,
0.78 mmol) and 4-(4-pyridinylmethyl)aniline (0.144 g, 0.78 mmol) in THF (5
mL)
was heated at the reflux temp. for 25 h. After cooling to room temp., the
resulting
solid was triturated with Et20 to afford the desired urea (0.25 g, 78%): mp
187-189
OC; TLC (50% EtOAc/50% pet. ether) Rf 0.04; 'H-NMR (DMSO-d,) 8 1.34 (s, 9H),
3.90 (s, 2H), 7.15 (d, J=7Hz, 2H), 7.20 (d, J=3 Hz, 2H), 7.40 (d, J=7 Hz,
2H), 7.80 (s
1H), 8.45 (dq J=3 Hz, 2H) 9.55 (s, 1H), 9.85 (s, IH), 12.50 (br s, 1H);
FAB-MS m/z
(rel abundance) 41 0 ((N4+H) +; 20%).

N
N N
H H
Step 3. N-(5-tert-Butyl thienyl)-N].(4.(4-pyridinylmethyl)phenyl)urea: A vial
containing N-(S-tert-butyl carboxy thienyl)-N]-(4-(4-pyridinyhnethyl)phenyl)-
urea (0.068 g, 0.15 mmol) was heated to 199 'C in an oil bath. After gas
evolution
ceased, the material was cooled and purified by preparative FIPLC (C-18
column;
gradient from 20% CH3CN/79.9% H20/0- 1 % TFA to 99.9% H20/0- 1 % TFA) to give
the desired product (0.024 g, 43%): TLC (50% EtOAc/50% pet. ether) Rf 0.18;
'H-
NMR (DMSO-d6) 8 1.33 (s, 9H), 4.12 (s, 2H), 6.77 (s, 1H), 6.95 (s, IH), 7.17
(d, J=9
Hz, 2H), 7.48 (d, J=9 Hz, 2H), 7.69 (d, J=7 Hz, 1H), 8.58 (s, 1H), 8.68 (d,
J=7 Hz,
io 2H)q 8.75 (s, 1H); EI-MS m1z 365 W).

A4b. Synthesis 3-Amino alkylthiophenes from 3-Amino alkyl thiophene-
carboxylate esters
NH3+ Cl-
5-tert-Butyl thiopheneammonium Chloride: To a solution of methyl 3-amino
tert-butyl thiophene-carboxylate (5.07 gq 23.8 mmol, 1.0 equiv) in EtOH (150
mL)
was added NaOH (2.0 g, 50 mmol, 2.1 equiv). The resulting solution was heated
at
the reflux temp. for 2.25 h. A cone. HO solution (approximately 10 mL) was
added
dropwise with stirring and the evolution of gas was observed. Stirring was
continued
for 1 h, then the solution was concentrated under reduced pressure. The white
residue
was suspended in EtOAc (150 mL) and a saturated NaHCO3 solution (150 n1L) was
added to dissolve. The organic layer was washed with water (150 mL) and a
saturated
NaCl solution (150 mL), dried (Na2SO4). and concentrated under reduced
pressure to
give the desired ammonium salt as a yellow oil (3.69 gq 100%). This material
was
used directly in urea formation without further purification.

A4c, Synthesis 3-Amino alkylthiophenes from N-BOC 3-Amino alkyl thiophenecarboxylate esters

0
NI_kO_Ik
MeO2 H
Step 1. Methyl 3-(tert-Butoxycarbonylamino) tert-butyl thiophenecarboxylate: To a solution of methyl 3-amino tert-butyl thiophenecarboxylate (150 g, 0.70 mol) in pyridine (2.8 L) at 5 'C was added di-tert-butyl dicarbonate (171.08 g,
0.78 mol, 1.1 equiv) and NN-dimethylaminopyridine (86 g, 0.70 mol, 1.00 equiv) and
the resulting mixture was stirred at room temp for 7 d. The resulting dark solution
was concentrated under reduced pressure (approximately 0.4 mmHg) at
io approximately 20 'C. The resulting red solids were dissolved in CH202 (3 L) and
sequentially washed with a 1 M H3PO4 solution (2 x 750 mL), a saturated NaHCO3
solution (800 mL) and a saturated NaCI solution (2 x 800 mL), dried (Na2SO4) and
concentrated under reduced pressure. The resulting orange solids were dissolved in
abs. EtOH (2 L) by warming to 49 'C, then treated with water (500 mL) to afford the
desired product as an off-white solid (163 g, 74%): 'H-NMR (CDC13) 8 1.38 (s, 9H),
1.51 (s, 9H), 3.84 (s, 3H), 7.68 (s, 1H), 9.35 (br s, 1H); FAB-MS m1z (rel abundance)
314 ((M+H)+] 45%).

0
N-]ko_]_k
H02 H
Step 2. 3-(tert-Butoxycarbonylamino) tert-butyl thiophenecarboxylic Acid.

2o To a solution of methyl 3-(tert-butoxycarbonylamino) tert-butyl thiophenecarboxylate (90.0 g, 0.287 mol) in THF (630 mL) and MeOH (630 mL) was
added a solution of NaOH (42.5 g, 1.06 mL) in water (630 mL). The resulting mixture was heated at 60 'C for 2 h, concentrated to approximately 700 mL under
reduced pressure, and cooled to 0 'C. The pH was adjusted to approximately 7 with a
1.0 N HO solution (approximately I L) while maintaining the internal temperature at
approximately 0 'C. The resulting mixture was treated with EtOAc (4 L). The pH
was adjusted to approximately 2 with a 1.0 N HO solution (500 mL). The organic
phase was washed with a saturated NaCl solution (4 x 1.5 L), dried (Na2SO4), and
concentrated to approximately 200 mL under reduced pressure. The residue was treated with hexane (1 L) to form a light pink (41.6 g). Resubmission of the mother
liquor to the concentration-precipitation protocol afforded additional product (38.4 g,
93% total yield): 'H-NMR (CDC13) 8 1.94 (s, 9H), 1.54 (s, 9H), 7.73 (s, IH), 9.19 (br
s, 1H); FAB-MS m1z (rel abundance) 300 ((M+H)+, 50%).

NH3+ Cl-
io Step 3, 5-tert-Butyl thiopheneammonium Chloride: A solution of 3-(tert-butoxycarbonylarnino) tert-butyl thiophenecarboxylic acid (3.0 g, 0.010 mol) in
dioxane (20 mQ was treated with an HO solution (4.0 M in dioxane, 12.5 mL, 0.050
mol, 5.0 equiv), and the resulting mixture was heated at 80 'C for 2 h. The resulting
cloudy solution was allowed to cool to room temp forming some precipitate. The
slurry was diluted with EtOAc (50 mL) and cooled to -20 'C. The resulting solids
were collected and dried overnight under reduced pressure to give the desired salt as
an off-white solid (1-72 g, 90%): 'H-NMR (DMSO-d,) 8 1.31 (s, 9H), 6.84 (d, J=1.48 Hz, 1H), 7.31 (d, J=1.47 Hz, 1H), 10.27 (br s, 3H).

2o A5. General Method for the Synthesis of BOC-Proteeted Pyrazoles
N
NH2
0
5-Amino tert-butyl-]V-(tert-butoxycarbonyl)pyrazole: To a solution of 5-amino-
3-tert-butylpyrazole (3.93 g, 28.2 mmol) in CH202 (140 ML) was added di-tert-butyl
dicarbonate (6.22 g, 28.5 mmol) in one portion. The resulting solution was stirred at
room temp. for 13 h, then diluted with EtOAc (500 mL). The organic layer was washed with water (2 x 300 mL), dried (MgSO4) and concentrated under reduced pressure. The solid residue was triturated (100 mL hexane) to give the desired
carbamate (6.26 g, 92%): mp 63-64 'C; TLC Rf (5% acetone/95% CH202); 'H-NMR (DMSO-d6) 5 1.15 (s, 9H), 1.54 (s, 9H), 5.22 (s, IH), 6.11 (s, 2H); FAB-MS m1z
((M+H)).

A6. General Method for the Synthesis of 2-Aminothiadiazoles
S
N
%N::kNH2
2-Amino (1-(I-ethyl)propyl)thiadiazine: To concentrated sulfuric acid (9.1 mL)
was slowly added 2-ethylbutyric acid (10.0 g, 86-mmol, 1.2 equiv). To this mixture
was slowly added thiosemicarbazide (6.56 g, 72 mmol, I equiv). The reaction mixture was heated at 85 OC for 7 h, then cooled to room temperature, and treated
with a concentrated NH40Hsolution until basic. The resulting solids were filtered to
afford 2-amino (1-(1-ethyl)propyl)thiadiazine product was isolated via vacuum filtration as a beige solid (6.3 g, 51%): mp 155-158 'C; TLC (5% MeOH/ 95% CHC13) Rf 0.14; 'H-NMR (DMSO-d6) 8 0.80 (t, J=7.35 Hz, 6H), 1 1.60 (in, 2H), 1 1.71 (in, 2H), 2 2.74 (m, IH), 7.00 (br s, 2H); HPLC ES-MS m1z 172 ((M+H)+).

2o A7, GeneralMethod for the Synthesis of 2-Aminooxadiazoles
0
N' NH2
H

Step 1. Isobutyric Hydrazide: A solution of methyl isobutyrate (10.0 g) and hydrazine (2.76 g) in MeOH (500 mL) was heated at the reflux. temperature over night
then stirred at 60 'C for 2 weeks. The resulting mixture was cooled to room temperature and concentrated under reduced pressure to afford isobutyric hydrazide as
a yellow oil (1.0 g, 10%), which was used inb the next step withour further purification.

N
%N::kNH2
Step 2. 2-Amino isopropyl oxadiazole: To a mixture of isobutyric hydrazide (0.093 g), KHCO3 (0. 102 g), and water (1 mL) in dioxane (1 mL) at room temperature
was added cyanogen bromide (O. IO g). The resulting mixture was heated at the refulx
temperature for 5 h, and stirred at room temperature for 2 d, then treated with C11202
(5 mL). The organic layer was washed with water (2 x 10 mL), dried (MgSO4) and
concentrated under reduced pressure to afford 2-amino isopropyl oxadiazole as a
white solid: BPLC ES-MS m1z 128 ((M+H)+).

io A8. General Method for the Synthesis of 2-Aminooxazoles
0
OH
Step 1. 3,3-Dimethyl-1-hydroxy butanone: A neat sample of 1-bromo-3,3-dimethyl butanone (33.3 g) at 0 'C was treated with a IN NaOH solution, then was
stirred for I h. The resulting mixture was extracted with EtOAc (5 x I 00 mL). The
combined organics were dried (Na2S04) and concentrated under reduced pressure to
give 3,3-dimethyl-1-hydroxy butanone (19 g, 100%), which was used inb the next
step withour further purification.

N
NH2
Step 2. 2-Amino4-isopropyl-1,3-oxazole: To a solution of 3,3-dimethyl-1-hydroxy butanone (4.0 g) and cyanimide (50% w/w, 2.86 g) in TBF (10 mL) was
added a IN NaOAc solution (8 mL), followed by tetra-n-butylammonium hydroxide (0.4 M, 3.6 mL), then a IN NaOH solution (1.45 mL). The resulting mixtuire was
stirred at room temperature for 2 d. The resulting organic layer was separated,
washed with water (3 x 25 mL), and the aqueous layer was extraced with Et20(3 x 25
mL). The combined organic layers were treated with a IN NaOH solution tuntil basic, then extracted with C11202 (3 x 25 mL). The combined organic layers were
dried (Na2SO4) and concentrated under reduced pressure to afford 2-Amino isopropyl- 1,3-oxazole (1.94 g, 41 %): HPLC ES-MS m1z 141 ((M+H)).

A9. Method for the Synthesis of Substituted aminotetrazoles
/N'N
Nl]'
Nj-'],NH2
To a solution of 5-aTninotetrazole (5 g), NaOH (2.04 g) and water (25 mL) in

EtOH
(1 15 niL) at the reflux temperature was added 2-bromopropane (5.9g). The resulting
mixture was heated at the reflux temperature for 6 d, then cooled to room temperature,
and concentrated under reduced pressure. The resulting aqueous mixture was washed
lo with CH2CI2 (3 x 25 mL), then concentrated under reduced pressure with the aid of a
Iyophlizer to afford a mixture of 1- and 2-isopropyl aminotetrazole (50%), which
was used without further purification: HPLC ES-MS m1z 128 ((M+H)+).

B, General Methods for Synthesis of Substituted Anilines
B1. General Method for Substituted Aniline Formation via Hydrogenation of a Nitroarene
N
H2NJD']]O]It
4-(4-Pyridinylmethyl)aniline: To a solution of 4-(4-nitrobenzyl)pyridine (7.0 g,
32.68 mmol) in EtOH (200 mL) was added 10% Pd/C (0.7 g) and the resulting slurry
was shaken under a H2 atmosphere (50 psi) using a Parr shaker. After I h, TLC and
'H-NMR of an aliquot indicated complete reaction. The mixture was filtered through
a short pad of Celitee. The filtrate was concentrated in vacuo to afford a white solid
(5.4 g, 90%): 'H-NMR (DMSO-d6) 8 3.74 (s, 2H), 4.91 (br s, 2H), 6.48 (d, J=8.46 Hz,
2H)] 6.86 (d] J=8.09 Hz, 2H), 7.16 (d5 J=5.88 Hz, 2H), 8.40 (d, J=5.88 Hz, 2H); El-
MS m1z 184 (M). This material was used in urea formation reactions without further
purification.

B2. General Method for Substituted Aniline Formation via Dissolving Metal Reduction of a Nitroarene
4-(2-Pyridinylthio)aniline: To a solution of 4-(2-pyridinylthio)-l-nitrobenzene
(Menai ST 3355A; 0.220 g, 0.95 nimol) and H20 (0.5 mL) in AcOH (5 mL) was added iron powder (0.317 g, 5.68 mmol) and the resulting slurry stirred for 16 h at
room temp. The reaction mixture was diluted with EtOAc (75 mL) and H20 (50 mL), basified to pH 10 by adding solid K2CO3 in portions (Caution: foaming). The
io organic layer was wa shed with a saturated NaCI solution, dried WgS04), concentrated in vacuo. The residual solid was purified by NTLC (30% EtOAc/70% hexane) to give the desired product as a thick oil (0.135 g, 70%): TLC (30% EtOAc/70% hexanes) Rf 0
B3a, General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction
0
02N OMe
Step 1. 1-Methoxy4-(4-nitrophenoxy)benzene: To a suspension of NaH (95%, 1.50 g, 59 mmol) in DNV (100 mL) at room temp. was added dropwise a solution of
2o 4-methoxyphenol (7.39 9, 59 mrnol) in DMF (50 mL). The reaction was stirred I h,
then a solution of 1-fluoro nitrobenzene (7.0 g, 49 mmol) in DMF (50 niL) was

added dropwise to form a dark green solution. The reaction was heated at 95 'C
overnight, then cooled to room temp., quenched with H20, and concentrated in vacuo.

The residue was partitioned between EtOAc (200 mL) and H20 (200 niL) . The organic layer was sequentially washed with H20 (2 x 200 mL), a saturated NaHCO3
solution (200 mL), and a saturated NaCl solution (200 mL), dried (Na2SO4), and
concentrated in vacuo. The residue was triturated (Et2O/hexane) to afford I-methoxy (4-nitrophenoxy)benzene (12.2 g, 100%): 'H-NMR (CDC13) 8 3.83 (s, 3H)q 6 7.04 (m, 6H), 8.18 (d9 J=9.2 Hz, 2H); EI-MS m1z 245 (M+).

H2N We
Step 2. 4-(4-Methoxyphenoxy)aniline: To a solution of 1-methoxy (4.

nitrophenoxy)benzene (12.0 g, 49 nunol) in EtOAc (250 mL) was added 5% Pt/C (1.5 g) and the resulting slurry was shaken under a H2 atmosphere (50 psi) for 18 h.

The reaction mixture was filtered through a pad of CeliteVwith the aid of EtOAc and
concentrated in vacuo to give an oil which slowly solidified (10.6 g, 100%): 'H-NMR
(CDC13) 5 3.54 (br s, 2H), 3.78 (s, 3H), 6.65 (d, J=8.8 Hz, 2H), 6 6.92 (m, 6H); El-
MS m1z 215 (M).

B3b. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction
CF3
02N
Step 1. 3-(Trifluoromethyl) (4-pyridinylthio)nitrobenzene: A solution of 4-1 5 mercaptopyridine (2.8 g, 24 mmoles), 2-fluoro nitrobenzotrifluoride (5 g, 23.5
mmoles), and potassium carbonate (6.1 g, 44.3 mmoles) in anhydrous DMF (80 mL)
was stirred at room temperature and under argon overnight. TLC showed complete
reaction. The mixture was diluted with Et2O (1 00 mL) and water (1 00 mL) and the
aqueous layer was back-extracted with Et2O (2 x 100 mL). The organic layers were
washed with a saturated NaCl solution (100 mL), dried (MgSO4), and concentrated
under reduced pressure. The solid residue was triturated with Et2O to afford the
desired product as a tan solid (3.8 g, 54%): TLC (30% EtOAc/70% hexane) Rf 0.06;
'H-NMR (DMSO-d6) 8 7.33 (dd, J=1.2,4.2 Hz, 2H), 7.78 (d, J=8.7 Hz, 1H), 8.46 (dd,
J=2.4, 8.7Hz, 1H), 8 8.56 (m, 3H).

CF3
ss']
H2N N
Step 2. 3-(Trifluoromethyl)4-(4-pyridinylthio)aniline: A slurry of 3-trifluoromethyl (4-pyridinylthio)nitrobenzene (3.8 g, 12.7 mmol), iron powder (4.0

g, 71.6 mmol), acetic acid (100 mL), and water (I mL) were stirred at room temp. for
h. The mixture was diluted with Et2O (I 00 niL) and water (1 00 mL). The aqueous
phase was adjusted to pH 4 with a 4 N NaOH solution. The combined organic layers
were washed with a saturated NaCl solution (100 mL), dried WgS04), and
concentrated under reduced pressure. The residue was filtered through a pad of silica
(gradient from 50% EtOAc/50% hexane to 60% EtOAc/40% hexane) to afford the
desired product (3.3 g): TLC (50% EtOAc/50% hexane) Rf 0.10; 'H-NMR (DMSO-
Q 8 6.21 (s, 2H), 6 6.87 (m, 3H), 7.10 (d, J=2.4 Hz, IH), 7.39 (d, J=8.4 Hz, IH),
8.29 (d, J=6.3 Hz, 2H).

io We. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction
SY11 S
02N N
Step 1. 4-(2-(4-Phenyl)thiazolyl)thio-l-nitrobenzene: A solution of 2-mercapto
phenylthiazole (4.0 g, 20.7 mmoles) in DMF (40 mL) was treated with 1-fluoro
1 5 nitrobenzene (2.3 mL, 21.7 mmoles) followed by K2CO3 (3.18 g, 23 mmol), and the
mixture was heated at approximately 65 'C overnight. The reaction mixture was then
diluted with EtOAc (100 mL), sequentially washed with water (100 mL) and a
saturated NaCI solution (100 mL), dried (MgSO4) and concentrated under reduced
pressure. The solid residue was triturated with a Et2O/hexane solution to afford the
2o desired product (6.1 g): TLC (25% EtOAc/75% hexane) Rf 0.49; 'H-NMR (CDC13) 8
7 7.47 (m. 3H), 7 7.63 (m, 3H), 7.90 (d, J=6.9 Hz, 2H), 8.19 (d, J=9.0 Hz, 2H).

SY1 S
H2N N
Step 2. 4-(2-(4-Phenyl)thiazolyl)thioaniline: 4-(2-(4-Phenyl)thiazolyl)thio-l-nitro-
benzene was reduced in a manner analagous to that used in the preparation of 3-
(trifluoromethyl) (4-pyridinylthio)aniline: TLC (25% EtOAc/75% hexane) Rf 0.18;
'H-NMR (CDC13) 8 3.89 (br s, 2H), 6 6.77 (m, 2H), 7 7.53 (m, 6H), 7 7.89 (m. 2H).

B3d. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction
0 rj]
02NJ:]r
Step 1. 4-(6-Methyl pyridinyloxy)-l-nitrobenzene: To a solution of 5-hydroxy-2-methylpyridine (5.0 g, 45.8 mmol) and 1-fluoro nitrobenzene (6.5 g, 45.8 mmol)
in anh DNT (50 mL) was added K2CO3 (13.0 g, 91.6 mmol) in one portion. The mixture was heated at the reflux temp. with stirring for 18 h and then allowed to cool
to room temp. The resulting mixture was poured into water (200 mL) and extracted
with EtOAc (3 x 150 mL). The combined organics were sequentially washed with

water (3 x I 00 mL) and a saturated NaCI solution (2 x 1 00 mL), dried (Na2SO4), and
concentrated in vacuo to afford the desired product (8.7 g, 83%). The this material
was carried to the next step without further purification.

ON N
H2NJ])r
Step 2. 4-(6-Methyl pyridinyloxy)aniline: A solution of 4-(6-methyl pyridinyloxy)-l-nitrobenzene (4.0 g, 17.3 mmol) in EtOAc (150 mL) was added to
10% Pd/C (0.500 g, 0.47 mmol) and the resulting mixture was placed under a H2 atmosphere (balloon) and was allowed to stir for 18 h at room temp. The mixture was
then filtered through a pad of Celite0and concentrated in vacuo to afford the desired
product as a tan solid (3.2 g, 92%): EI-MS m1z 200 (m).

We. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction
0 OMe
02N OMe
Step 1. 4-(3,4-Dimethoxyphenoxy)-l-nitrobenzene: To a solution of 3,4-dimethoxyphenol (1.0 g, 6.4 mmol) and 1-fluoro nitrobenzene (700 jIL, 6.4 mmol)
in anh Dl]ff (20 mL) was added K2CO3 (1.8 g, 12.9 mmol) in one portion. The mixture was heated at the reflux temp with stirring for 18 h and then allowed to cool
to room temp. The mixture was then poured into water (I 00 mL) and extracted with
EtOAc (3 x 100 mL). The combined organics were sequentially washed with water (3
We
H2N We
Step 2. 4-(3,4-Dimethoxyphenoxy)aniline: A solution of 4-(3,4]dimethoxy-phenoxy)-l-nitrobenzene (0.8 g, 3.2 mmol) in EtOAc (50 ML) was added to 10% Pd/C (0. I 00 g) and the resulting mixture was placed under a H2 atmosphere (balloon)
and was allowed to stir for 18 h at room temp. The mixture was then filtered through
a pad of Celite(& and concentrated in vacuo to afford the desired product as a white
lo solid (0.6 g, 75%): EI-MS m1z 245 (M).

BU General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction
N
02N
Step 1, 3-(3-Pyridinyloxy)-l-nitrobenzene: To a solution of 3-hydroxypyridine (2.8 g, 29.0 mmol), 1-bromo nitrobenzene (5.9 g, 29.0 mmol) and copper(I) bromide (5.0 g, 34.8 mmol) in anh DMT (50 mL) was added K2CO3 (8.0 g, 58.1 mmol) in one portion. The resulting mixture was heated at the reflux temp. with
stirring for 18 h and then allowed to cool to room temp. The mixture was then poured
into water (200 mL) and extracted with EtOAc (3 x 150 mL). The combined organics
were sequentially washed with water (3 x 100 mL) and a saturated NaCl solution (2 x
100 mL), dried (Na2SO4), and concentrated in vacuo. The resulting oil was

purified
by flash chromatography (30% EtOAc/70% hexane) to afford the desired product (2.0
g, 32 %). This material was used in the next step without fin-ther purification.

N
H2N OfIJI
Step 2. 3-(3-Pyridinyloxy)aniline: A solution of 3]-(3-pyridinyloxy)-1-nitrobenzene (2.0 & 9.2 mmol) in EtOAc (100 mL) was added to 10% Pd/C (0.200 g)
and the resulting mixture was placed under a H2 atmosphere (balloon) and was allowed to stir for 18 h at room temp. The mixture was then filtered through a pad of
B3g. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction
N
02N
Step 1. 3-(5-Methyl pyridinyloxy)-1-nitrobenzene: To a solution of 3-hydroxy-5-methylpyridine (5.0 g, 45.8 mmol), 1-bromo nitrobenzene (12.0 g, 59.6 mmol) and copper(I) iodide (10.0 g, 73.3 mmol) in anh DMF (50 mL) was added K2CO3 io (13.0 g, 91.6 mmol) in one portion. The mixture was heated at the reflux temp. with
stirring for 18 h and then allowed to cool to room temp. The mixture was then poured
into water (200 mL) and extracted with EtOAc (3 x 150 mL). The combined organics
were sequentially washed with water (3 x 100 mL) and a saturated NaCl solution (2 x
100 mL), dried (Na2SO4), and concentrated in vacuo . The resulting oil was purified
by flash chromatography (30% EtOAc/70% hexane) to afford the desired product (1.2
g, 13%).

N
H2N
Step 2. 3-(5-Methyl pyridinyloxy)-1-nitrobenzene: A solution of 3-(5-methyl pyridinyloxy)-1-nitrobenzene (1.2 g, 5.2 mmol) in EtOAc (50 mL) was added to 10%
Pd/C (0. I 00 g) and the resulting mixture was placed under a H2 atmosphere (balloon)
and was allowed to stir for 18 h at room temp. The mixture was then filtered through
a pad of Celitee and concentrated in vacuo to afford the desired product as a red oil
(0.9 g, 86%): CI-MS m1z 201 ((M+H)+).

B3h, General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction
0
IC I
02N
Step 1. 5-Nitro (4-methylphenoxy)pyridine: To a solution of 2-chloro nitropyridine (6.34 g, 40 mmol) in DW (200 mL) were added of 4-methylphenol (5.4
1*9 42 Ceo) HoX poppr srm (qm OZ) jN(j snojpAqm U! (lourtu L-c 49 9-0) 3pjxo Qj).ioddw pim (louitu 1-9 62 0-1) ouoqdou
.41ouio.iq-E %ou-nu log T Zol !omdo/008)
louoqdon 17

poglu-tr jo uolinjos r oL :au;azuaqoillu-l-(oiqllAuaiqj,-E)- I dalS
NzO 9z
uollanpan Sq pamolloa luoi njjjsqnS 3i viaoiV ai ilqdoal3nbj q3noiqjL uoi
umlol
.1 R 11, .1
allalgOllIN VIA U01 Vtal0A auil!uV painillsqnS ioj poqlaw le-lauaf) *!Ea
R
1%001 +W) (oourpunqu
10.0 zlul SW-Ig !(HI 4zH LgeZ=C 'P) ETS '(HI 'zH WS 'LgeZ=f 4PP) 9tp*S '(HZ
OZ
'zH 60*8=F'P) 610L '(HI 'zH Z8]8=f 4P) VO*L '(HZ 'zH 917*8=,r 6P) 86*9 IHE
's) 9Z*Z
2 (9P-0SWG) IdM-Hj tZt7eo -f-d (nipa lad %og/oVoig %og) DrjL !(oop) Do 0 1
Z-80Z
duI :(%Z6 49 gg,L) lonpoid pausop Qqj ZAIS ol oVolaql!m poqsum pug palwEdos
sum
olulldiowd Sui Insai oql -osimdorp poppr s-om olu.41U oqj ol poppv srm ozig
ui IDI-I
jo uoilnlos V ol!loo jo prd r qSnoiql paiollU sm aiMxiui uoi ovai oqjL -q
g-Zioj gi
pomis Alsnoio2iA svA pim oizqdsomir zH -0 iopun pooold uaqj sum aitnxiw uoT
ovai
aq,L *(2 09*0) Dipcl %01 ql!m polvail uzql uogm qlltA poSind srm (qw 061)
OV01a
u! (qm 01) H01H PUB (bg I '10ulEu OE T V6-9) Ou'PLL]d(XxouoqdlSqlc)w-t)-Z-
oj4!u
-g uoilnlos V :apjiojq-3oapSq!(j auipliSd(Sxouaqdlgqlaui-t)-Z-ouimV-S -Z dalS
ol
+WH .10
-10%) +H
'(,(H+W)) I CZ (00uuPunqv 101) z/w SW-EIVJ !(HI 'zH 96'Z=r'P) 66*8 IHI 'zH
Z808
'tp6]Z=r 4PP) 89*8 '(HZ 'zH 60&8=r'p) t?Z*L '(HI 'zH OZ06=r'P) 6I&L 4(HZ'zH
9t7]8=r
'P) 80*L 'WE 4s) IE'Z 2 OP-OSIARD UM-H, t6L6O -d (.ioqlo lad %oL/oVojq %OC)
Drjj!D,Z8-08dui :(%gL'Sgo[L)IonpoidpaiisopgqlgAISOI(lMgZ).ioqloladpuu g
Nm 9Z) -1QTuM'(quI 9Z) u0ljnl0s H09M X Iuqj!m polqwm Alluiluonbas pug polmdos
oiam spljos oqj pue 'q I ioj pom s srm 3jmxiui si
qjL -ojuj!diooid u 0jriou02? ol (qtu
009) jolum qwA polvan sum omilxitu Sutllnsoi oqj -dtuol tuooi it! jq2RUQA0
POMIS
SUM QnljXlui QqL '(AMbO g*1 41OUIM 09 T 8Z*8) EODZ'X PtM (AlnbO 5Z'l 41OUIEU
Og
0809Z/86Sfl/JL3d I II ZC/66 OM
S
]] CS
H2NJ::]
io Step 2, 4-(3-Thienylthio)aniline: 4-(3-Thienylthio)-1-nitrobenzene was
reduced to
the aniline in a manner analogous to that described in Method B 1.

B3j. General Method for Substituted Aniline Formation via Nitroarene
Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction
0
N
H2N N
4-(5-Pyrimininyloxy)aniline- , 4-Aminophenol (1.0 g, 9.2 mmol) was dissolved
in
DMF (20 mL) then 5-bromopyrimidine (1.46 g, 9.2 mmol) and K2CO3 (1-9 9, 13.7
mmol) were added. The mixture was heated to 100 'C for 18 h and at 130 'C for

48 h
2o at which GC-MS analysis indicated some remaining starting material. The reaction
mixture was cooled to room temp. and diluted with water (50 mL). The resulting
solution was extracted with EtOAc (100 mL). The organic layer was washed with a
saturated NaCl solution (2 x 50 mL), dried (MgSO4), and concentrated in vacuo. The
residular solids were purified by MPLC (50% EtOAc/50% hexanes) to give the
desired amine (0.650 g, 38%).

Wk. General Method for Substituted Aniline Formation via Nitroarene
Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction
Br We
N
CZ&9) SI-01SA10 M011OX P-I0JJV 01 (QuRxQq/3v0ja POZI ISAJO oc
. it,
swA ljo utAojq Irnp!soj axU -omssaid poonpaiiapun poir.4mmoo ptm (VOSS pau
YD . p
sutA -IOAE1 Oung-IO QU '(1m 9L x Z) OV019 TPA POl3V-4x0 PuR (qm 9Z) -MIUM
lp!M
POI 4 UOqj 4jqSjEUOAO Do 96 01 POTBOXI SWA O'Mxlum 1101 OvO-I Oq1 -OSXILL]S
EIA POPPE
SwA QOunu 8z 6qm C) ouozuaqo4juoionU-t7 cq I joj -dtuol uiooi ju mis ol
pomoll-B
srm ojmxltu SuilInsai oqL -(qm 001) jW(j ul (joujLU 8Z gg-C) oul Ljxcux0jpOju
gz
P.

-Z-,KxO-IPXq-9 JO uOljn1Os v POPPE SUM (qm 00 1) AING quu 111 (IOUILU Ztr 'S
0- I '%L6)
jVM JO funjs paulls v oj. :auazuaqoil!u-I-Axo(ISpliSd(Sxoqjaw-Z)-S)-t7 *E
dalS
OV40 N NzO
Tg*Z) po molloX snoosiA 10 OATS ol amssaid poonpai
.iopun polu.4mmoo pur (troSzEN) pou
p wom sjokel omRio pouiqluoo oqL -(qw 001 oz
x Z) Ozlg TPA PO10V-4xz 110111 u0'jn10s IDH N1 oql!m pazil'unnou summkol
snoonbv
oqj -dtual tuooi ol looo ol pomollu uzqj sEm oMxlui uoilorai oqL -q I iqj
-duiol
xnUoi oqj ol poluoiq uoql pue unu OCioj -dmaj Luooi ol poumm srm ainixitu
uoil 00.1
pjqjr4 XjjqSjjs puu molloX Sul Insai Qqj -ftm og -xoidd-e !%OE) uoi jos
Qp!xo.13d
in
uogo.ipX,q v pu-u QOuRu LL' IL 'qm 9Z) u0111110s HOEM N Z v JO Qmxiui v qjjm
polvall
sEm put D. o oi po=m sTtA am-qxiui uoijorai o2tmio I-qi?!jq oqL -q Z
Ituoilippt
ue joj pom!js sm omi1xim Sul Insai oql pue 02UUXS ETA POPP-0 SUM QOURU Z*Zq
'IM
90*L) olvioq jj(qjoui!jjL 917 -10J Do 8L- 1-8 -Ills 01 POMOHE sum oimxnu Sul
Insai
.1
OT Ptm Qs'tAdO-IP (10umn 8-1L 'Im L-8Z !ouExgq u! W g-Z) uoi njos tunn
.1 . p!IIA4nq
-u uE POPPE sTM Do 8L- It! (qm 9LO MI III (1OuRu 6-L17 'S 6-8)
OulpuAdAxoiqjotu ol

-Z-oTuo.iq-g JO uoi Os paui s v oL :auip1.xSdSxoql0tu-Z-Sx0-'PAH-S eZ dajS
.Inj
N
avqo-]]]/]OH
'Lg.ofx (Otmxoq
%06/DV019%01)DrIl:(PIOIA%96'Sl]t7)11001!lUIOA'AxolloAolud'BOAI OlAmssaid
P0011PO-I -IOPun P01 41IO01100 Puu ('70SzrN) Poup wom sioSvI om.Rio pouiqLuoo
g
Oq6L *(qM 001 X Z) OV01a tp!M POj3V-1lX0 PUR (qtU 0g).IajVtA ql!M POIVO.4 SUM
OJMXIT.U
uoi orai oq.L -dTual uioo-i oi looo oi pomol1v uoql 'q Zt7.IOJ JOSSOA UOI owl
P01-80S r UR
Do OL TV POTBOXI MA (qm 09) HOQW u! (10unu 9*69 429CE) OMEN PuB QOuRu ZOZZ
g-g) ou!p!jAdouioiq!p-g'Z JO om,4xitu V :auip!.iSdSxoqjatu-Z-omo.1jj-S el
dajS
0809Z/86Sfl/13d Os; I II U/66 OM
B4a. General Method for Substituted Aniline Synthesis via Nucleophilic
Aromatic Substitution using a Halopyridine
] N
H2NJasl)]
3-(4-Pyridinylthio)aniline: To a solution of 3-aminothiophenol (3.8 ML, 34
mmoles)
I 0 in anh DMF (90mL) was added 4-chloropyridine hydrochloride (5.4 g, 35.6
mmoles)
followed by K2CO3 (16.7 g, 121 mmoles). The reaction mixture was stirred at
room
temp. for 1.5 h, then diluted with EtOAc (100 mL) and water (100mL). The
aqueous
layer was back-extracted with EtOAc (2 x 100 mL). The combined organic layers
were washed with a saturated NaCl solution (100 mL), dried (MgS04), and
concentrated under reduced pressure. The residue was filtered through a pad
of silica
(gradient from 50% EtOAc/50% hexane to 70% EtOAc/30% hexane) and the
resulting material was triturated with a Et2O/hexane solution to afford the
desired
product (4.6 g, 66%): TLC (100 % ethyl acetate) Rf 0.29; 'H-NMR (DMSO-d6) 8
5.41
(s, 2H), 6 6.74 (m, 3H), 7.01 (d, J=4.8, 2H), 7.14 (t, J=7.8 Hz, 1H), 8.32
(d, J=4.8,
2o 2H).

B4b. General Method for Substituted Aniline Synthesis via Nucleophilic
Aromatic Substitution using a Halopyridine
H2N
4-(2-Methyl pyridinyloxy)aniline: To a solution of 4-aminophenol (3.6 g, 32.8
mmol) and 4-chloropicoline (5.0 g, 39.3 mmol) in anh DMPU (50 mL) was added
potassium tert-butoxide (7.4 g, 65.6 mmol) in one portion. The reaction
mixture was
heated at 100 'C with stirring for 18 h, then was allowed to cool to room
temp. The
resulting mixture was poured into water (200 mL) and extracted with EtOAc (3
x 150
B4c. General Method for Substituted Aniline Synthesis via Nucleophilic
Aromatic Substitution using a Halopyridine
Me
02N--O-ri
io Step 1, Methyl(4-nitrophenyl) pyridylamine: To a suspension of N-methyl
nitroaniline (2.0 g, 13.2 mmol) and K2CO3 (7.2 g, 52.2 mmol) in DMPU (30mL)
was
added 4-chloropyridine hydrochloride (2.36 g, 15.77 mmol). The reaction

mixture
was heated at 90 T for 20 h, then cooled to room temperature. The resulting mixture
was diluted with water (100 mL) and extracted with EtOAc (100 mL). The organic
layer was washed with water (100 mQ, dried (Na2SO4) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel,
gradient from 80% EtOAc /20% hexanes to 100% EtOAc) to afford methyl(4-nitrophenyl) pyridylamine (0.42 g)
Me
H2N--O-fi
Step 2. Methyl(4-aminophenyl)4-pyridylamine: Methyl(4-nitrophenyl) pyridylamine was reduced in a manner analogous to that described in Method B 1.

B5. General Method of Substituted Aniline Synthesis via Phenol Alkylation Followed by Reduction of a Nitroarene
S
0 N
2
Step 1. 4-(4-Butoxyphenyl)thio-l-nitrobenzene: To a solution of 4-(4-nitrophenyl-
thio)phenol (1.50 g, 6.07 mmol) in anh DW (75 ml) at 0 'C was added NaH (60% in
mineral oil, 0.267 g, 6.67 mmol). The brown suspension was stirred at 0 'C until gas
t7 pm polqsvtA AlIvIluonbras I(qm OOZ) ozig tpyA poltili se ltu
.p m ojmx Sulllnsoi oql OE
qj.ioj-duiajxnUo.ioqjjlopojm UO!10-eO.IQTPUupopp'BSUtA(AlnbQZO'O'IOURUCO*E'g
Rs
t7qqeo)oj,uuoq-mot jAjnq-paj-j 1,guoi ppV
.P P M
oqj pojao!pu! DjL oun qov
.1 .4m ju 'q E ioj -dwol xnUoi aip jr polinq sum ojmxlui
uOllouQ.l QlqL](qm 01) JHL qm u! (lounu 1-51 42 OC-E) alruoqjuoi
1,44nC[-;.ia;
.P
-jp Jo uoilnlos -o poppe siam duiol tuooi ju (qm 05) dHL qEM U! QOURU 1051 oo]E) 9Z
am umi a
.pouajAqiou-i-,tr'tp Jo uot os -e ojL :;auilluu(lAzuaqlSouluqlya3sxoln - al jnj
H
0y N NzH
0
soualluoululul(l
jo uoi ulSaV aqj Aq sam iuV palnl!lsqnS jo sisaqjuSS ioj poqlaN junuaf) ogg
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%EC) 01,L :(Z dolS 'qEjj poqloW) oui um(oT
.qllXui LL]d-t)-t?-QxqjoTuo.IonU]4)
P.

-C Jo uoi mdoid otp ui posn jrqj ol snoSvIvue iouu-uui u ui ouillim oqj ol poonpai
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sum ouozuoqo.4ju- I -oT S I 9 tF 17
.ql(lXuzqclAxolng-.V)-i7:;auil!uuoiql(I uaqd xo n Zd S

0 NzH 91
S
6(HZ'zHL*8=r'P)15*L '(HZ
'zH6=r'P)LI*L 6(HZ'zHL'8=F'P)80*L '(HZ6zH9*9=rgi)io,tr '(HZ4Tu)0L*1 '(HZ
'zH5*L=r'xoqdd,u)Zt7*j '(HE4zHg'L=,r4l)Z6*02(9P-OSW(I)UWM-H, !9L f-d
(OlluxQ11 %08/3V019 %OZ) DU :(%L9 'S tpZ-1) p!los molloA le sT lonpoid otp
OA12 01
(ouexo,q %05/oVoig %og ol ouuxoq %08/oVola %OZ uiog luo!pua) AqduBojouioxq-3
ol
lo2 uoi is Aq pog]md s-em q-3i
.qm '1!0 M011OX =13 V OA12 ol Qmssoid poonpai
.iopun poiriluomoo pu-c 'QoSSW) pou
. p I(qw 00j7 x Z) nim pm poiqsrm wom
someRio poq!qtuo3 oql -(qw oog x Z) ozig ippA polouilxo sum ojmxiiu Suilinsai
oiql
-(qW 0017) -10IRM JO UOT Ippi! oqj Aq poqouonb sum uoql 4-dwol tuooiq 9
peuoij!pptv
uu paulls sTtA uoi orai oqL -poppr wom (lounu trEE-0 Tua El) Hum -pug (ATnbQ
9
go-o 41ounu CoCoo 4qm 5EO,o Tui 9g) ouulnqopoi Iruoi!ppu puu Ilouoqd pajoranm
Jo omosaid zqj pol-em DqL otup qou
.4m ju q 81 -ioj *dTuol uiooi ju pom s sum
.Pui
UOI 3-00J Oqj, 'Do 0 1-0 UTT.U 51 lQAO osimdojp poppv sum, (qw OZ) jW(I quo
ui (lounu
LO*9 41111 069* T Zl*l) ou-einqopoi Jo uoilnlos tv uoqj l(u!tu gl) poddols
uoilnIOAQ
0809V86Sfl/13d I II U/66 OM
saturated NaHCO3 solution (100 MI), water (100 mL) and a saturated NaCl
solution
(50 mL), dried (MgSO4), and concentrated under reduced pressure. The
resulting
white solid was purified by silica gel chromatography (gradient from 33%
EtOAc/67% hexane to 50% EtOAc/50% hexane) to afford the desired product as a
white solid (2.09 g, 46%): TLC (50% EtOAc/50% hexane) Rf 0.45; 'H-NMR
(DMSO-d6) 5 1.43 (s, 9H), 3.63 (s, 2H), 4.85 (br s, 2H), 6.44 (d, J=8.4 Hz,
2H),
6.80 (d, J=8.1 Hz, 2H), 7.00 (d, J=8.4 Hz, 2H), 7.28 (d, J=8.1 Hz, 2H), 9.18
(br s,
1H); FAB-MS m1z 298 (M+).

io B7, General Method for the Synthesis of Aryl Amines via Electrophilic
Nitration Followed by Reduction
N
02NJO]]
Step 1. 3-(4-Nitrobenzyl)pyridine: A solution of 3-benzylpyridine (4.0 g,
23.6 nunol) and 70% nitric acid (30 mL) was heated overnight at 50 'C. The
resulting
mixture was allowed to cool to room temp. then poured into ice water (350
mL). The
aqueous mixture then made basic with a IN NaOH solution, then extracted with
Et2O
(4 x 100 mL). The combined extracts were sequentially washed with water (3 x
100
mL) and a saturated NaCl solution (2 x 100 mL), dried (Na2SO4), and
concentrated in
vacuo. The residual oil was purified by MPLC (silica gel; 50 % EtOAc/50%
hexane)
then recrystallization (EtOAc/hexane) to afford the desired product (1.0 g,
22%): GC-

MS m1z 214 (M).

N
H 2 N
Step 2. 3-(4-Pyridinyl)methylaniline: 3-(4-Nitrobenzyl)pyridine was reduced to the
aniline in a manner analogous to that described in Method B 1.

B8. General Method for Synthesis of Aryl Amines via Substitution with Nitrobenzyl Halides Followed by Reduction
NL
02NJ::r N
Step 1. 4-(I-Imidazolylmethyl)-l-nitrobenzene: To a solution of imidazole (0.5 g,
7.3 mmol) and 4-nitrobenzyl bromide (1.6 g, 7.3 mmol) in anh acetonitrile (30 mL)
was added K2CO3 (1.0 g, 7.3 mmol). The resulting mixture was stirred at rooom temp. for 18 h and then poured into water (200 n1L) and the resulting aqueous solution
wasextracted with EtOAc (3 x 50 mL). The combined organic layers were sequentially washed with water Q x 50 mL) and a saturated NaCl solution (2 x 50
lo mL), dried (MgSO4), and concentrated in vacuo. The residual oil was purified by
MPLC (silica gel; 25% EtOAc/75% hexane) to afford the desired product (1.0 g, 91 %): EI-MS m1z 203 (M).

H2NJ:::r N
Step 2. 4-(l-Imidazolylmethyl)aniline: 4-(I-Imidazolylrnethyl)-l-nitrobenzene was
reduced to the aniline in a manner analogous to that described in Method B2.

B9. Formation of Substituted Hydroxymethylanilines by Oxidation of Nitrobenzyl Compounds Followed by Reduction
OH
02N N
Step 1, 4-(l-Hydroxy-l-(4-pyridyl)methyl-l-nitrobenzene: To a stiffed solution
of 3-(4-nitrobenzyl)pyridine (6.0 g, 28 mmol) in C11202 (90 mL) was added m-CPBA
(5.80 g, 33.6 mmol) at 10 'C, and the mixture was stirred at room temp. over-night.

The reaction mixture was successively washed with a 10% NaHS03 solution (50 mL),
a saturated K2CO3 solution (50 mL) and a saturated NaCl solution (50 mL), dried
(MgSO4) and concentrated under reduced pressure. The resulting yellow solid (2.68
g) was dissolved in anh acetic anhydride (30 mL) and heated at the reflux temperature
overnight. The mixture was concentrated under reduced pressure. The residue was
dissolved in MeOH (25 mL) and treated with a 20% aqueous NH3 solution (30 mL).

The mixture was stirred at room temp. for I h, then was concentrated under reduced
pressure. The residue was poured into a mixture of water (50 niL) and CH202 (50

mL). The organic layer was dried (MgSO4), concentrated under reduced pressure,
and purified by column chromatography (80% EtOAc/ 20% hexane) to afford the desired product as a white solid. (0.53 g, 8%): mp 110-118 'C; TLC (80% EtOAc/20% hexane) Rf 0.12; FAB-MS m1z 367 ((M+H)+] 100%).

OH
H2N N
Step 2. 4-(1-Hydroxy-1-(4-pyridyl)methylaniline: 4-(1-Hydroxy-1-(4-pyridyl)-io methyl-1-nitrobenzene was reduced to the aniline in a manner analogous to that
described in Method B3d, Step2.

B10. Formation of 2-(N-methylcarbamoyl)pyridines via the Menisci reaction
0
CI NH2
N
Step 1, 2-(N-methylcarbamoyl) chloropyridine. (Caution: this is a highly hazardous, potentially explosive reaction.) To a solution of 4-chloropyridine (10.0 g)
in N-methylformamide (250 mL) under argon at ambient temp was added conc.

H2SO4 (3.55 niL) (exotherm). To this was added H202 (17 mL, 30% wt in H20) followed by FeS04'7H20 (0.55 g) to produce an exotherm. The reaction was stirred
in the dark at ambient temp for 1h then was heated slowly over 4 h at 45 'C. When
bubbling subsided,the reaction was heated at 60 'C for 16 h. The opaque brown solution was diluted with H20 (700 mL) fol.lowed by a 10% NaOH solution (250 mL). The aqueous mixture was extracted with EtOAc (3 x 500 rnL) and the organic
layers were washed separately with a saturated NaCl solution (3 x 150 mIL. The
combined organics were dried (MgSO4) and filtered through a pad of silica gel eluting
with EtOAc. The solvent was removed in vacuo and the brown residue was purified
by silica gel chromatography (gradient from 50% EtOAc / 50% hexane to 80% EtOAc / 20% hexane). The resulting yellow oil crystallized at 0 'C over 72 h to give
2-(N-methylcarbamoyl) chloropyridine in yield (0.61 g, 5.3%): TLC (50% 3o EtOAc/50% hexane) Rf 0.50; MS; 'H NMR (CDC13): d 8.44 (d, 1 H, J = 5.1 Hz, CHN), 8.21 (s, 1H, CHCCO), 7.96 (b s, 1H, NH), 7.43 (dd, IH, J = 2.4, 5.4 Hz, CICHCN), 3.04 (d9 3H, J = 5.1 Hz, methyl); CI-MS m1z 171 ((M+H)+).

B11. Generalmethod for the Synthesis of (o-Sulfonylphenyl Anifines
0
Me
'S,
02N
0]]O
Step 1. 4-(4-Methylsulfonylphenoxy)-1-nitrobenzene: To a solution of 4-(4-methylthiophenoxy)-1-ntirobenzene (2 gg 7.66 mmol) in CH202 (75 mL) at 0 'C was
slowly added mCPBA (57-86%, 4 g), and the reaction mixture was stirred at room
temperature for 5 h. The reaction mixture was treated with a I N NaOH solution (25
io mL). The organic layer was sequentially washed with a 1N NaOH solution (25 mL),

water (25 mL) and a saturated NaCl solution (25 mL), dried (MgSO4), and concentrated under reduced pressure to give 4-(4-methylsulfonylphenoxy)-1-nitrnbenzene as a solid (2.1 g).

Step 2. 4-(4-Methylsulfonylphenoxy)-1-aniline: 4-(4-Methylsulfonylphenoxy)-1-nitrobenzene was reduced to the aniline in a manner anaologous to that described in
Method 133d, step 2.

B12. General Method for Synthesis of (o-Alkoxy-o)-carboxyphenyl Anilines
0
0 Ome
02NJcr OMe
Step 1. 4-(3-Methoxycarbonyl4-methoxyphenoxy)-1-nitrobenzene: To a solution of -(3-carboxy hydroxyphenoxy)-1-nitrobenzene (prepared in a manner analogous to that described in Method B3a, step 1, 12 mmol) in acetone (50 ML) was added
K2CO3 (5 g) and dirnethyl. sulfate (3.5 mL). The resulting mixture was heated aaaaaat
the reflux tempoerature overnight, then cooled to room temperature- and filtered
through a pad of Celiteo. The resulting solution was concentrrated under reduced
pressure, absorbed onto silica gel, and purified by column chromatography (50%
EtOAc / 50% hexane) to give 4-(3-methoxycarbonyl methoxyphenoxy)-1-nitrobenzene as a yellow powder (3 g): mp 1 1 5 118 'C.

0 OH
02NJ:]r OMe
Step 2. 4-(3-Carboxy4-methoxyphenoxy)-1-nitrobenzene: A mixture of 4-(3-methoxycarbonyl methoxyphenoxy)-1-nitrobenzene (1.2 g), KOH (0.33 g),and water (5 mL) in MeOH (45 mL) was stirred at room temperature overnight and then
heated at the reflux temperature for 4 h. The resulting mixture was cooled to room
temperature and concentrated under reduced pressure. The residue was dissolved in
water (50 mL), and the aqueous mixture was made acidic with a 1N HCl solution.

The resulting mixture was extracted with EtOAc (50 mL). The organic layer was dried (MgSO4) and concentrated under reduced pressure to give 4-(3-carboxy io methoxyphenoxy)-1-nitrobenzene (1.04 g).

C. General Methods of Urea Formation
Cla. Reaction of a Heterocyclic Amine with an Isocyanate
0 0
N)] Nicr]]C
H H
N-(5-tert-Butyl thienyl)-N]-(4-phenoxyphenyl)urea: To a solution of 5-tert-butyl thiophene-ammonium chloride (prepared as described in Method A4b; 7.28 g,
46.9 mmol, 1.0 equiv) in anh DW (80 mL) was added 4-phenoxyphenyl isocyanate (8.92 g, 42.21 mmol, 0.9 equiv) in one portion. The resulting solution was stirred at
50-60 'C overnight, then diluted with EtOAc (300 mL). The resulting solution was
sequentially washed with H20 (200 mL), a 1 N HCl solution (50 mL) and a saturated

NaCl solution (50 mL), dried (Na2SO4), and concentrated under reduced pressure.

The resulting off-white solid was recrystallized (EtOAc/hexane) to give a white solid
(13.7 g, 88%), which was contaminated with approximately 5% of bis(4-phenoxyphenyl)urea. A portion of this material (4.67 g) was purified by Rash chromatography (9% EtOAc/27% CH202/64% cyclohexane) to afforded the desired product as a white solid (3.17 g).

Clb, Reaction of a Heterocyclic Arnine with an Isocyanate
0
N
N)] N
H H
N-(3-tert-Butyl isoxazolyl)-N]-(4-phenoxyphenyl)urea: To a solution of 5-amino tert-butylisoxazole (8.93 g, 63.7 mmol, 1 eq.) in CH202 (60 mL) was added
4-phenyloxyphenyl isocyanate (15.47 g, 73.3 mmol, 1.15 eq.) dropwise. The mixture
was heated at the reflux temp. for 2 days, eventually adding additional CH202 (80
mL). The resulting mixture was poured into water (500 mL) and extracted with Et2O
(3 x 200 mL). The organic layer was dried (MgSO4) then concentrated under reduced
pressure. The residue was recrystallized (EtOAc) to give the desired product (15.7 g,
io 70%): mp 182-184 IC; TLC (5% acetone/95% acetone) Rf 0.27; 'H-NMR (DMSO-d6)
8 1.23 (s, 9H), 6.02 (s, 1H), 6.97 (dd, J=0.2, 8.8 Hz, 2H), 6.93 (d, J=8.8 Hz, 2H), 7.08
(t, J=7.4 Hz, 1H), 7.34 (m, 2H), 7.45 (dd, J=2.2, 6.6 Hz, 2H) , 8.80 (s, 1H), 10.04 (s,
IH); FAB-MS m1z (rel abundance) 352 ((M+H)+,70%).

C1c. Reaction of a Heterocyclic Arnine with an Isocyanate
0 0
N)] N
H H
N-(3-tert-Butyl pyrazolyl)-N]-(4-(4-methylphenyl)oxyphenyl)urea: A solution of 5-amino tert-butylpyrazole (0.139 g, 1.0 mmol, 1.0 equiv) and 4-(4-methylphenoxy)phenyl isocyanate (0.225 g, 1.0 mmol 1.0 equiv) in toluene (10 mL)
was heated at the reflux temp. overnight. The resulting mixture was cooled to room
temp and quenched with MeOH (a few mL). After stirring for 30 min, the mixture
was concentrated under reduced pressure. The residue was purified by prep. HPLC
(silica, 50% EtOAc/50% hexane) tQ give the desired product (0.121 g, 33%): mp 204
IC; TLC (5% acetone/95% CH202) Rf 0.92; 'H-NMR (DMSO-d6) 8 1.22 (s, 9H),
2.24 (s, 3H), 5.92 (s, IH), 6.83 (d, J=8.4 Hz, 2H), 6.90 (d, J=8.8 Hz, 2H), 7.13 (d,
J=8.4 Hz, 2H), 7.40 (d, J=8.8 Hz, 2H), 8.85 (s, 1H), 9.20 (br s, IH), 11.94 (br s, 1H);
EI-MS m1z 364 (M+).

CId. Reaction of a Heterocyclic Amine with an Isocyanate

0
N]A'N CI
H H CI
N-(5-tert-Butyl thienyl)-N]-(2,3-dichlorophenyl)urea: Pyridine (0.163 mL, 2.02
mmol) was added to a slurry of 5-tert-butylthiopheneammonium chloride (Method A4c; 0.30 g, 1.56 nunol) and 2,3-dichlorophenyl isocyanate (0.32 mL]- 2.02 mmol) in
CH202 (10 mL) to clarify the mixture and the resulting solution was stirred at room
io temp. overnight. The reaction mixture was then concentrated under reduced pressure
and the residue was separated between EtOAc (15 mL) and water (15 mL). The organic layer was sequentially washed with a saturated NaHCO3 solution (I 5 mL), a
1N HO solution (15 mL) and a saturated NaCl solution (15 mL), dried (Na2SO4), and
concentrated under reduced pressure. A portion of the residue was by preparative
HPLC (C-18 column; 60% acetonitrile/40% water/0.05% TFA) to give the desired urea (0.180 gg 34%): mp 169-170 'Q TLC (20% EtOAc/80% hexane) Rf 0.57; 'H.

NMR (DMSO-d6) 8 1.31 (s, 9H), 6.79 (s, 1H), 7.03 (s, IH), 7 7.33 (m, 2H), 8.16
(dd, J=1.84, 7.72 Hz, IH), 8.35 (s, 1H), 9.60 (s, 1H); 13C_NMR (DMSO_d6) 8 31.9
(3Q9 34.09 103.4] 116.1] 119.3] 120.0] 123.4] 128.19 131.6] 135.62 138.1, 151.72 155.2;
FAB-MS m1z (rel abundance) 343 ((M+H)+, 83%)] 345 ((M+H+2)+] 56%)] 347 ((M+H+4)+g 12%).

Cle. Reaction of a Heterocyclic Amine with an Isocyanate
0 CI
N% K
N N CI
H H
N-(3-tert-Butyl pyrazolyl)-N]-(3,4-dichlorophenyl)urea: A solution of 5-amino-
3-tert-butyl-]V'-(tert-butoxycarbonyl)pyrazole (Method A5; 0.150 g, 0.63 mmol) and
,4-dichlorophenyl isocyanate (0.118 gj 0.63 mmol) were in toluene (3.1 mL) was
stirred at 55 'C for 2 d. The toluene was removed in vacuo and the solid was redissolved in a mixture of CH202 (3 mL) and TFA (1.5 mL). After 30 min, the solvent was removed in vacuo and the residue was taken up in EtOAc (10 mL). The
resulting mixture was sequentially washed with a saturated NaHCO3 solution (10 mL)
arid a NaCl solution (5 mL), dried (Na2SO4), and concentrated in vacuo. The residue
was purified by flash chromatography (gradient from 40% EtOAc/ 60% hexane to 55%EtOAc/ 5% hexane) to give the desired product (0.102 g, 48%): mp 182-184 'C;
TLC (40% EtOAc/60% hexane) Rf 0.05, FAB-MS m1z 327 ((M+H)+).

C2a. Reaction of a Heterocyclic Amine with Phosgene to Form an Isocyanate, then Reaction with Substituted Aniline
N
0 N=C=O
Step 1. 3-tert-Butyl isoxazolyl Isocyanate: To a solution of phosgene (20% in

toluene, 1.13 mL, 2.18 nunol) in CH2CI2 (20 mL) at 0 'C was added anh. pyridine
(0.176 mL, 2.18 mmol), followed by 5-amino tert-butylisoxazole (0.305 g, 2.18 mmol). The resulting solution was allowed to warm to room temp. over I h, and then
was concentrated under reduced pressure. The solid residue dried in vacuo for 0.5 h.

S-]n
N 0
N)]N
H H
Step 2. N-(3-tert-Butyl isoxazolyl)-N]-(4-(4-pyridinylthio)phenyl)urea: The crude 3-tert-butyl isoxazolyl isocyanate was suspended in anh toluene (10 mL) and
4-(4-pyridinylthio)aniline (0.200 g, 0.989 mmol) was rapidly added. The suspension
was stirred at 80 'C for 2 h then cooled to room temp. and diluted with an EtOAc/CH2CI2 solution (4:1, 125 mL). The organic layer was washed with water (100 mL) and a saturated NaCl solution (50 mL), dried (MgSO4), and concentrated
under reduced pressure. The resulting yellow oil was purified by column chromatography (silica gel, gradient from 2% MeOH/98% CH202 to 4% MeOH/6% CH2CI2) to afford a foam, which was triturated (Et2O/hexane) in combination with
sonication to give the product as a white powder (0.18 g, 49%): TLC (5% C2b. Reaction of a Heterocyclic Amine with Phosgene to Form an Isocyanate Followed by Reaction with Substituted Aniline
N N=C=O
Step 1. 5-tert-Butyl isoxazolyl Isocyanate: To a solution of phosgene (148 mL,
1.93 M in toluene, 285 mmol) in anhydrous CH202 (1 L) was added 3-amino tert-io butylisoxazole (10.0 g, 71 mmol) followed by pyridine (46 mL, 569 mmol). The
mixture was allowed to warm to room temp and stirred overnight (ca. 16 h), then
mixture was concentrated in vacuo. The residue was dissolved in anh. THF (350 mL)
and stirred for 10 min. The orange precipitate (pyridinium hydrochloride) was removed and the isocyanate-containing filtrate (approximately 0.2 M in THF) was
used as a stock solution: GC-MS (aliquot obtained prior to concentration) m1z 166
0
N N Nj:]r
H H
Step 2. N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-pyridinylthio)phenyl)urea: To a solution of 5-tert-butyl isoxazolyl isocyanate (247 mL, 0.2 M in THF, 49.4 mmol)
was added 4-(4-pyridinylthio)aniline (5 g, 24.72 mmol), followed by THF (50 mL)
then pyridine (4.0 mL, 49 mmol) to neutralize any residual acid. The mixture was
stirred overnight (ca. 18 h) at room temp. Then diluted with EtOAc, (300 mL). The
organic layer was washed successively with a saturated NaCI solution (100 mL), a
saturated NaHCO3 solution (100 mL), and a saturated NaCI solution (100 mL), dried
WgS04), and concentrated in vacuo. The resulting material was purified by

MPLC
(2 x 300 g silica gel, 30 % EtOAc/70% hexane) to afford the desired product as a
white solid (8.24 g, 90 %): mp 178-179 'C; 'H-NMR (DMSO-d6) 8 1.28 (s, 9H), 6.51
9,W) I gCoottepung
101 z1ul SW-I9 !(HI 's Iq) 009ZI '(HI 's Iq) 5Z]6 '(HI 4s Iq) Z6*8 '(HZ 'zH 9Z*9=Ar'P)
EVS '(HZ 'zH Z*6=f 'P) Eg*L '(HZ 'zH Z8*8=f 'P) 0 1 *L '(HZ 6zH gZ49=r 6P) 88*9 '(HI Oz
4S) L6*9 '(H6 's) VVI 2 (9P-0SWG) 'UM-H, !6EZ-0 f-d (EIDHD %06 /HOQW. %01)
Dq,L!'QP Do SZZ< duI:(%69'S 6CI*0) P0111 PO-IlsOP 0111 P.IOJJu ol (.iolqlo -jod %og/ozig
%0g) poqsrm sem p1los oli 0
.qm oql -ol-el!di aid mou r uuoj ol 1q I ioj -duiol uiooi
IV -Ps 01 POtAO1113 WC u0ljnl0s 13H MI -0 Ul POAJOSSIP wom spps oqjL -oji!j!diooid
01111M v Sululj0J q ZI JOJ Do OL 1-0 P31-9011 s-gAk QMxTui uOl 3rQJ Qql Ptm jonbil-e gi
QuO ul POPRO sWA Q0uRU L9-0 'S 091-0) oloz-e.L]d(IKuoqmoxxolnq-ldal)-,N-I,,4nq
1al-c-outum-g lKunIs MP 01 *(qm L) ouonjol ui popuodsns srm p1los olp4m oqj uzql onam ul polr4ttoottoo slem uoilnlos SuilInsai oT4,L -q I IOAO -diual Ulow ol ULMA*i
ol pamoll'o sem uolql 4iq I ioj Do 0 1v p3m s sum uoilnlos olql -nodd-o olioloo mollof,
luolsuril 4e Suisnuo jonbilp ouo ui poppL7 svA Qouitu E- 1 62 OgZ-0) out m(XxolxulppAd of
--V)-tT U01P 'UITU g E IQAO XIMOIS POPPU SIVA (qM gol-0) out uM poppr
P.

XImOls SWA Do 0 It (qtu C 1) zlDzHD sno-ipXqm u! (qm 8*9 tuonjol ui W6- 1) oua2solqd
jo uminjos -e oiL :uain(iguaqd(AxolSuip!.iid-tp)-tp)-,AT-(IAlozuigd-S-14na-lial-E)-)V
H H H
N Ny N N%
anq
juy papillsqnS qllm uoijauaX gq7pamolloa g
alnucAml uv taioA ol aua2soqd q;lm auituV 3113S 131aH 9 JO 110113 a Z
'(,W) 89E zlzu SW-Ia !(HI 4s) l9e6 IHI 4s) 0 1 #6 '(HZ 6zH 9Z*9=,r 4P) U*8
'(HZ 'zH E8*8=f 'P) Z9*L '(HZ 4zH Z8*8=r V) ZgeL '(HZ 'zH 9Z'9=f 6P) 9669
'(HI 4s)
0809V86Sfl/lDd C9 1 1 1 U/66 OM
-']]
N 0
N)] N
H H
N-(3-tert-Butyl-1-methyl pyrazolyl)-N]-(4-(4-pyridinyloxy)phenyl)urea: To a solution of 5-amino tert-butyl-1-methylpyrazole (189 g, 1.24 mol) in anh. CH202
(2.3 L) was added NN'-carbonyldiimidazole (214 g, 1.32 mol) in one portion. The
mixture was allowed to stir at ambient temperature for 5 h before adding 4-(4-
pyridinyloxy)aniline. The reaction mixture was heated to 36 'C for 16 h. The resulting mixture was cooled to room temp, diluted with EtOAc (2 L) and washed
lo with H20 (8 L) and a saturated NaCl solution (4 L). The organic layer was dried

(Na2SO4) and concentrated in vacuo. The residue was purified by crystallization
(44.4% EtOAc/44.4% Et2O/11.2% hexane, 2.5 L) to afford the desired urea as a white
solid (230 g, 51%): mp 149-152 'C; 'H-NMR (DMSO-d,) 8 1.18 (s, 9H), 3.57 (s, 3H), 6.02 (s, 1H), 6.85 (d, J=6.0 Hz, 2H), 7.08 (d, J=9.0 Hz, 2H), 7.52 (d, J=9.0 Hz,
2H)q 8.40 (d5 J=6.0 Hz, 2H), 8.46 (s, 1H), 8.97 (s, 1H); FAB-LSIMS m1z 366 ((M+H]).

C3b, Reaction of a Heterocyclic Amine with NN]-Carbonyldiimidazole Followed by Reaction with a Substituted Aniline
0 S N
N N
H H
N-(3-tert-Butyl pyrazolyl)-N]-(3-(4-pyridinylthio)phenyl)urea: To a solution of
5-amino tert-butyl-]V'-(tert-butoxycarbonyl)pyrazole (0.282 g, 1.18 mmol) in CH202 (1.2 mL) was added NN-carbonyldiimidazole (0.200 g, 1.24 mmol) and the mixture was allowed to stir at room temp. for I day. 3-(4-Pyridinylthio)aniline (0.239
g, 1.18 mmol) was added to the reaction solution in one aliquot and the resulting
mixture was allowed to stir at room temp. for 1 day. Then resulting solution was
treated with a 10% citric acid solution (2 mL) and was allowed to stir for 4 h. The
organic layer was extracted with EtOAc (3 x 15 mL), dried (MgSO4), and concentrated in vacuo. The residue was diluted with C11202 (5 mL) and trifluoroacetic acid (2 mQ and the resulting solution was allowed to stir for 4 h. The
trifluoroacetic reaction mixture was made basic with a saturated NaHCO3 solution,
then extracted with CH202 (3 x 15 mL). The combined organic layers were dried (MgSO4) and concentrated in vacuo. The residue was purified by flash chromatography (5% MeOH/95% CH202). The resulting brown solid was triturated with sonication (50% Et2O/50% pet. ether) to give the desired urea (0.122 g, 28%).

mp >224 'C dec; TLC (5% MeOH/ 95% CHC13) Rf 0.067; 'H-NMR (DMSO-d6) 8 1.23 (s, 9H), 5.98 (s, IH), 7.04 (drn, J=13.24 Hz, 2H), 7 7.19 (m, 1H), 7 7.47
io (m, 2H), 7 7.82 (m, IH), 8.36 (dm, J=15.44 Hz, 2H), 8.96 (br s, 1H), 9.32 (br s,
IH), 11.97 (br s, 1H); FAB-MS m/z (rel abundance) 368 QvI% 100%).

C4a. Reaction of Substituted Aniline with NN-Carbonyldiimidazole Followed by Reaction with a Heterocyclic Amine
N N
0
N N
H H
N-(3-tert-Butyl-1-methyl pyrazolyl)-N]-(4-(4-pyridinylmethyl)phenyl)urea: To a solution of 4-(4-pyridinylrnethyl)aniline (0.200 g, 1.08 mmol) in CH202 (10 ML)
was added NN-carbonyldiimidazole (0.200 g, 1.23 mmol). The resulting mixture was stirred at room tempe for 1 h after which TLC analysis indicated no starting
2o aniline. The reaction mixture was then treated with 5-amino tert-butyl-1-methylpyrazole (0. 165 g, 1.08 mmol) and stirred at 40-45 'C overnight. The

reaction
mixture was cooled to room temp and purified by column chromatography
(gradient
from 20% acetone/80% CH202 to 60% acetone/40% CH202) and the resulting solids
were crystallized (Et2O) to afford the desired urea (0.227 g, 58%): TLC (4%
MeOH/96% CH202) Rf 0-15; 'H-NMR (DMSO-d6) 8 1.19 (s, 9H), 3.57 (s, 3H), 3.89
(s, 2H), 6.02 (s, IH), 7.14 (d, J=8.4 Hz, 2H), 7.21 (d, J=6 Hz, 2H), 7.37 (d,
J=8.4 Hz,
2H)] 8 8.42 (m. 3H), 8.81 (s. IH); FAB-MS m1z 364 (M+H)+).

N
N%
N N 0
H H H
N-(3-tert-Butyl pyrazolyl)-N]-(3-(2-benzothiazolyloxy)phenyl)urea: A solution
of 3-(2-benzothiazolyloxy)aniline (0.24 g, 1.0 mmol, 1.0 equiv) and N.N'-
carbonyldiimidazole (0.162 g, 1.0 mmol, 1.0 equiv) in toluene (10 mL) was
stirred at
room temp for 1 h. 5-Amino tert-butylpyrazole (0.139 g, 1.0 mmol) was added
and
the resulting mixture was heated at the reflux temp. overnight. The resulting
mixture
was poured into water and extracted with CH202 (3 x 50 mL). The combined
organic
layers were concentrated under reduced pressure and dissolved in a minimal
amount
of CH202- Petroleum ether was added and resulting white precipitate was
resubmitted to the crystallization protocol to afford the desired product
(0.0 1 5 g, 4%).

mp 1 10-1 I 1 'C; TLC (5% acetone/95% CH202) Rf 0.05;'H-NMR (DMSO-d6) 8 1.24
(s, 9H), 5.97 (s, 1H), 7 7.04 (m, 1H), 7 7.44 (m, 4H), 7.68 (d, J=5.5 Hz,
1H),
7.92 (d] J=7.7 Hz, IH), 7.70 (s, 1H), 8.95 (s, 1H), 9.34 (br s, 1H), 11.98
(br s, IH);
EI-MS m1z 408 (M).

C4c. Reaction of a Heterocyclic Amine with Phosgene to Form an Isocyanate
Followed by Reaction with Substituted Aniline
0 0
N
N)] N<)]
H H
N-(5-tert-Butyl thienyl)-N]-(4-(4-pyridinyloxy)phenyl)urea: To an ice cold
solution phosgene (1.93M in toluene; 0.92 mL, 1.77 mmol) in CH202 (5 mL) was
added a solution of 4-(4-pyridinyloxy)aniline (0.30 g, 1.61 mmol) and
pyridine (0.255
g, 3.22 mmol) in CH202 (5 mL). The resulting mixture was allowed to warm to
room
temp. and was stirred for I h, then was concentrated under reduced pressure.
The
residue was dissolved in CH202 (5 mL), then treated with 5-tert-
C5, General Method for the Reaction of a Substituted Aniline with
Triphosgene Followed by Reaction with a Second Substituted Amine
0
N)]N
H H
N-(3-tert-Butyl4-methyl isoxazolyl)-N]-(2-fluorenyl)urea: To a solution of
triphosgene (55 mg, 0.185 mmol, 0.37eq) in 1,2-dichloroethane (I.OmL) was
added a

solution of 5-amino methyl tert-butylisoxazole (77.1 mg, 0.50 mmol, 1.0 eq) and
diisopropylethylamine (0.104 mL, 0.60 mmol, 1.2 eq) in 1,2-dichloroethane (1.0 mL).

The reaction mixture was stirred at 70 'C for 2 h, cooled to room temp., and treated
with a solution of 2-aminofluorene (30.6 mg, 0.50 mmol, 1.0 eq) and
diisopropylethylamine (0.087 mL, 1.0 eq) in 1,2-dichloroethane (1.0 mL). The
reaction mixture was stirred at 40 'C for 3 h and then at RT for 17 h to produce a
precipitate. The solids were washed with Et2O and hexanes to give the desired urea as
a beige solid (25 mg, 14%): mp 179-181 'C; 'H-NMR (DMSO-d6) 5 1.28 (s, 9H),
2.47 (s, 3H), 3.86 (s, 2H), 7.22 (t, J=7.3 Hz, IH), 7.34 (m, 2H), 7.51 (d, J=7.3 Hz,
IH)] 7.76 (m. 3H), 8.89 (s, IH), 9.03 (s, IH); HPLC ES-MS m/z 362 ((M+H)+).

S
N 3/
Step 1. 5-Methyl]azidocarbonyl)thiophene: To a solution of 5-Methyl
thiophenecarboxylic acid (1.06 g, 7.5 nunol) and Et3N (1.25 mL, 9.0 mmol) in
acetone (50 mL) at -10 'C was slowly added ethyl chloroforinate (1.07 mL, 11.2
mmol) to keep the internal temperature below 5 'C. A solution of sodium azide (0.83
io g, 12.7 mmol) in water (6 mL) was added and the reaction mixture was stirred for 2 h
at 0 'C. The resulting mixture was diluted with C11202 (10 mL) and washed with a
saturated NaCl solution (10 mL). The aqueous layer was back-extracted with CH202
(10 mL), and the combined organic layers were dried (MgSO4) and concentrated in
vacuo. The residue was purified by column chromatography (10% EtOAc/ 90%
hexanes) to give the azidoester (0.94 g, 75%). Azidoester (100 mg, 0.6 nimol) in
anhydrous toluene (10 mL) was heated to reflux for I h then cooled to rt. This
solution was used as a stock solution for subsequent reactions.

OCN S
_1 :]/
Step 2. 5-Methyl thiophene Isocyanate: 5-Methyl (azidocarbonyl)thiophene
(0.100 g5 0.598 mmol) in anh toluene (10 mL) was heated at the reflux temp. for 1 h
then cooled to room temp. This solution was used as a stock solution for subsequent
reactions.

0
N N)] N j]J
H H
Step 3. N-(5-tert-Butyl isoxazolyl)-N]-(5-methyl thienyl)urea: To a solution
of 5-methyl thiophene isocyanate (0.598 mmol) in toluene (10 rnL) at room temp.

was added 3-amino tert-butylisoxazole (0.092 g, 0.658 mmol) and the resulting
mixture was stirred overnight. The reaction mixture was diluted with EtOAc (50 mL)

and sequentially washed with a 1 N HO solution (2 x 25 mL) and a saturated NaCl
solution (25 rnL), dried (MgSO4), and concentrated under reduced pressure. The
residue was purified by WLC (20% EtOAc/80% hexane) to give the desired urea
(0.156 g, 93%): mp 200-201 'C; TLC (20% EtOAc/80% hexane) Rf 0.20; EI-MS mlz
368 (M).

C7. General Methods for Urea Formation by Curtius Rearrangement and Isocyanate Trapping

C
CHO

Step 1. 3-Chloro4,4-dimethylpent enal: POC13 (67.2 mL, 0.72 mol) was added to cooled (O 'C) DMF (60.6 mL, 0.78 mol) at rate to keep the internal temperature
io below 20 'C. The viscous slurry was heated until solids melted (approximately 40
IC), then pinacolone (37.5 mL, 0.30 mol) was added in one portion. The reaction
mixture was then to 55 'C for 2h and to 75 'C for an additional 2 h. The resulting
mixture was allowed to cool to room temp., then was treated with THF (200 mL) and
water (200 mL), stirred vigorously for 3 h, and extracted with EtOAc (500 mL). The
organic layer was washed with a saturated NaCl solution (200 mL), (hied (Na2SO4)
and concentrated under reduced pressure. The residue was filtered through a pad of
silica (CH202) to give the desired aldehyde as an orange oil (15.5 g, 35%): TLC (5%
EtOAc/95% hexane) Rf 0.54; 'H NMR (CDC13) d 1.26 (s, 9H), 6.15 (d, J=7.0 Hz,
IH)] 10.05 (d] J=6.6 Hz, IH).

S
C02Me

Step 2. Methyl 5-tert-butyl thiophenecarboxylate: To a solution of 3-chloro-4,4-dimethylpent enal (1.93 g, 13.2 mmol) in anh. DUT (60 mL) was added a solution of Na2S (1.23 g, 15.8 mmol) in water (10 mL). The resulting mixture was
stirred at room temp. for 15 min to generate a white precipitate, then the slurry was
treated with methyl bromoacetate (2.42 g, 15.8 mmol) to slowly dissolve the solids.

The reaction mixture was stirred at room temp. for 1.5 h, then treated with a 1 N HCI
solution (200 mL) and stirred for 1 h. The resulting solution was extracted with
EtOAc (300 n1L). The organic phase was sequentially washed with a I N HCI
solution (200 mL), water (2 x 200 mL) and a saturated NaCl solution (200 mL), dried
S
C02H

Step 3. 5-tert-Butyl thiophenecarboxylic acid: Methyl 5-tert-butyl thiophenecarboxylate (0.10 g, 0.51 mmol) was added to a KOH solution (0.33 M in
90% MeOH/10% water, 2.4 mL, 0.80 mmol) and the resulting mixture was heated at
io the reflux temperature for 3 h. EtOAc (5 mL) was added to the reaction

mixture, then
the pH was adjusted to approximately 3 using a 1 N HCl solution. The resulting
organic phase was washed with water (5 mL), dried (Na2SO4), and concentrated under
reduced pressure (0.4 mmHg) to give the desired carboxylic acid as a yellow solid
(0.067 g, 73%): TLC (20% EtOAc/79.5% hexane/0.5% AcOH) Rf 0.29; 'H NMR
(CDC13) 8 1.41 (s, 9H), 6.89 (d, J=17 Hz, 1H), 7.73 (d, J=3.7 Hz, 1H), 12.30 (br s,
1H); 13C NMR (CDC13) 8 32.1 (3Q] 35.2] 122.9] 129.21 135.1, 167.5, 168
S 0
N)] N CI
H H CI
Step 4. N-(5-tert-Butyl thienyl)-N]-(2,3-dichlorophenyl)urea: A mixture of 5-
tert-butyl thiophenecarboxylic acid (0.066 g, 0.036 mmol), DPPA (0.109 g, 0.39
mmol) and Et3N (0.040 g, 0.39 mmol) in toluene (4 mL) was heated to 80 'C for 2 h,
2,3-dichloroaniline (0. 1 16 g5 0.72 mmol) was added, and the reaction mixture was
heated to 80'C for an additional 2 h. The resulting mixture was allowed to cool to
room temp. and treated with EtOAc (50 mL). The organic layer was washed with a 1
N HCI solution (3 x 50 mL), a saturated NaHCO3 solution (50 mL), and a saturated
NaCl solution (50 mL), dried (Na2SO4), and concentrated under reduced pressure.

The residue was purified by column chromatography (5% EtOAc/95% hexane) to
afford the desired urea as a purple solid (0.030 g, 24%): TLC (10% EtOAc/90%
hexane) Rf 0.28; 'H NMR (CDC13) 5 1.34 (s, 9H), 6.59 (br s, 2H), 7 7.13 (m. 2H),
.66 (br s, 1H), 8.13 (dd, J=2.9, 7.8 Hz, IH); C NMR (CDC13) 8 32.2 (3Q] 34.6]
117.4, 119.0', 119.1'] 119.29 121.5, 124.4, 127.61 132.69 135.2, 136.6,
153.4; HPLC
ES-MS m1z (rel abundance) 343 ((M+H)+, 100%)5 345 ((M+H+2)+] 67%), 347
((M+H+4)+j14%).

C8. Combinatorial Method for the Synthesis of Diphenyl Ureas Using Triphosgene
One of the anilines to be coupled was dissolved in dichloroethane (O. IO M). This
solution was added to a 8 mL vial (0.5 mL) containing dichloroethane (1 mL). To this
was added a triphosgene solution (0. 12 M in dichloroethane, 0.2 mL, 0.4 equiv.),
followed by diisopropylethylamine (0.35 M in dichloroethane, 0.2 mL, 1.2 equiv.).

The vial was capped and heat at 80 T for 5 h, then allowed to cool to room temp for
approximately 10 h. The second aniline was added (0.10 M in dichloroethane, 0.5
mL, 1.0 equiv.), followed by diisopropylethylamine (0.35 M in dichloroethane, 0.2
mL, 1.2 equiv.). The resulting mixture was heated at 80 'C for 4 h, cooled to room
temperature and treated with MeOH (0.5 mL). The resulting mixture was

concentrated under reduced pressure and the products were purified by reverse phase
HPLC.

2o D, Misc. Methods of Urea Synthesis
DI. Electrophylic Halogenation
0
N N[:.

Br H H
N-(2-Bromo tert-butyl thienyl)-N]-(4-methylphenyl)urea: To a slurry of N-(5-tert-butyl thienyl)-N]-(4-methylphenyl)urea (0.50 g, 1.7 mmol) in CHC13 (20 mL)
at room temp was slowly added a solution of Br2 (0.09 mL, 1.7 mmol) in CHC13 (10
mL) via addition funnel causing the reaction mixture to become homogeneous.

Stirring was continued 20 min after which TLC analysis indicated complete reaction.

The reaction was concentrated under reduced pressure, and the residue triturated (2 x
Et2O/hexane) to give the brominated product as a tan powder (0.43 g, 76%): mp 161-
163 OC; TLC (20% EtOAc/ 80% hexane) Rf 0.71; 'H NMR (DMSO-d6) 8 1.29 (s, 9H), 2.22 (s, 3H), 7.07 (d, J=8.46 Hz, 2H), 7.31 (d, J=8.46 Hz, 2H), 7.38 (s, 1H), 8.19
(s, IH), 9.02 (s, IH); C NMR (DMSO.d,) 8 20.3, 31.6 (3Q, 34.7,
89.6,117.5,118.1
(2Qq 129.2 (2Q9 130.89 136.09 136.9, 151.8, 155.2; FAB-MS m/z (rel abundance) 367
((M+H)+7 98%)] 369 (M+2+H)+g I 00%).

D2, Synthesis of o)-Alkoxy Ureas
0 0
N)]N H
H H
Step 1. N-(5-tert-Butyl thienyl)-N]-(4-(4-hydroxyphenyl)oxyphenyl)urea: A solution of N-(5-tert-butyl thienyl)-N-(4-(4-methoxyphenyl)oxyphenyl)urea (1.2 g,
3 mmol) in CH202 (50 mL) was cooled to -78 'C and treated with BBr3 (1.0 M in io CH202] 4.5 mL. 4.5 mmol, 1.5 equiv) dropwise via syringe. The resulting bright
yellow mixture was warmed slowly to room temp and stirred overnight. The resulting
mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL), then washed with a saturated NaHCO3 solution (50 mL) and a saturated NaCI solution (50 mL), dried (Na2SO4), and concentrated under reduced
pressure. The residue was purified via flash chromatography (gradient from 10%
EtOAc/90% hexane to 25% EtOAc/75% hexane) to give the desired phenol as a tan foam (1.1 g, 92%): TLC (20% EtOAc/80% hexane) Rf 0.23; 'H NMR (DMSO-d6) 8
1.30 (s, 9H), 6 6.84 (m, 7H), 6.97 (d, J=1.47 Hz, IH), 7.37 (dm, J=9.19 Hz, 2H),
8.49 (s, 1H), 8.69 (s, 1H), 9.25 (s, IH); FAB-MS m1z (rel abundance) 383 ((M+H)+,
2o 33%).

0 0

N)]N
H H
Step 2. N-(5-tert-Butyl thienyl)-N]-(4-(4-ethoxyphenyl)oxyphenyl)urea: To a mixture of N-(5-tert-butyl thienyl)-N]-(4-(4-hydroxyphenyl)oxyphenyl)urea (0.20
gq 0.5 mmol) and CS2CO3 (0.18 gq 0.55 mmol, 1.1 equiv) in reagent grade acetone (10
mL) was added ethyl iodide (0.08 mL, 1.0 mmol, 2 equiv) via syringe, and the resulting slurry was heated at the reflux temp. for 17 h. The reaction was cooled,
filtered, and the solids were washed with EtOAc. The combined organics were concentrated under reduced pressure, and the residue was purified via preparative
HPLC (60% CH3CN/40% H20/0.05% TFA) to give the desired urea as a colorless powder (0. 1 6 g, 73%): mp 155-156 'C; TLC (20% EtOAC/ 80% hexane) Rf 0.40; 'H-
NMR (DMSO-d6) 5 1.30 (s, 9H), 1.30 (t, J=6.99 Hz, 3H), 3.97 (q, J=6.99 Hz, 2H),
6.80 (d, J=1.47 Hz, 1H), 6.86 (dm, J=8.82 Hz, 2H), 6.90 (s, 4H), 6.98 (d, J=1.47, IH),
7.40 (dm, J=8.83 Hz, 2H), 8.54 (s, 1H), 8.73 (s, IH); 13C_NMR (DMSO-d,) 8 14.7,
32.0 (3Q9 33.91 63.39 102.59 115.5 (2Q9 116.3] 118.4 (2Q9 119.7 (2C), 119.8 (2Q]
135.09 136.39 150.49 152.19 152.49 154.4, 154.7; FAB-MS m1z (rel abundance) 411
((M+H)+] 15%).

io D3. Synthesis of o)-Carbamoyl Ureas
N 0 0
zz]'
N K NJ:DrIaN)t]]
H H H
N-(3-tert-Butyl-1-methyl pyrazolyl)-N]-(4-(4-
acetaminophenyl)methylphenyl)urea: To a solution of N-(3-tert-butyl-1-methyl pyrazolyl)-N]-(4-(4-aminophenyl)methylphenyl)urea (0.300 g, 0.795 mmol) in i5 CH202 (15 mL) at 0 'C was added acetyl chloride (0.057 ML, 0.795 mmol), followed
by anhydrous Et3N (0. III mL, 0.795 mmol). The solution was allowed to warm to
room temp over 4 h, then was diluted with EtOAc (200 mL). The organic layer was
sequentially washed with a 1M HO solution (125 mL) then water (100 mL), dried (MgSO4), and concentrated under reduced pressure. The resulting residue was purified by filtration through a pad of silica (EtOAc) to give the desired product as a
white solid (0.160 g, 48%): TLC (EtOAc) Rf 0.33; 'H-NMR (DMSO-d6) 8 1.17 (s, 9H)q 1.98 (s, 3H), 3.55 (s, 3H), 3.78 (s, 2H), 6.00 (s, 1H), 7.07 (d, J=8.5 Hz, 2H), 7.09
(d, J=8.5 Hz, 2H), 7.32 (d, J=8.5 Hz, 2H), 7.44 (d, J=8.5 Hz, 2H), 8.38 (s, IH), 8.75
(s, 1H), 9.82 (s, 1H); FAB-MS m1z 420 ((M+H)+).

D4. General Method for the Conversion of Ester-Containing Ureas into Alcohol-Containing Ureas
0
N)]N CI
H H CI
N-()V-(2-Hydroxyethyl) tert-butyl pyrazolyl)-N]-(2,3-dichlorophenyl)urea.

A solution of N-(]V'-(2-(2,3-dichlorophenylamino)carbonyloxyethyl) tert-butyl pyrazolyl)-N'-(2,3-dichlorophenyl)urea (prepared as described in Method A.3; 0.4 g,
0.72 mmoles) and NaOH (0.8 mL, 5N in water, 4.0 minoles) in EtOH (7 ML) was 'heated at -65 'C for 3 h at which time TLC indicated complete reaction. The reaction
io mixture was diluted with EtOAc (25 mL) and acidified with a 2N HO solution (3
mL). The resulting organic phase was washed with a saturated NaCl solution (25
mL), dried (MgSO4) and concentrated under reduced pressure. The residue was crystallized (Et20) to afford the desired product as a white solid (0. 17 g, 64 %): TLC
(60% EtOAc/40% hexane) Rf 0.16; 1H-NMR (DMSO-d6) 8 1.23 (s, 9H), 3.70 (t, J=5.7 Hz, 2H), 4.10 (t7 J=5.7 Hz, 2H), 6.23 (s, 1H), 7 7.32 (in, 2H), 8 8.09 (in,
1H), 9.00 (br s, IH), 9.70 (br s, 1H); FAB-MS m1z (rel abundance) 371 ((M+H)+]
100%).

D5a. General Method for the Conversion of Ester-Containing Ureas into 2o Amide-Containing Ureas

Step 1. N-(N'-(Carboxymethyl) tert-butyl pyrazolyl)-N]-(2,3-dichlorophenyl)urea: A solution of N-(IV'-(ethoxycarbonylinethyl) tert-butyl pyrazolyl)-N'-(2,3-dichlorophenyl)urea (prepared as described in Method A3, 0.46 g,
1. 1 1 mmoles) and NaOH (1.2 mL, 5N in water, 6.0 mmoles) in EtOH (7 niL) was stirred at room temp. for 2 h at which time TLC indicated complete reaction. The
reaction mixture was diluted with EtOAc (25 mL) and acidified with a 2N HO solution (4 mL). The resulting organic phase was washed with a saturated NaCl solution (25 mL), dried (MgSO4) and concentrated under reduced pressure. The residue was crystallized (Et20/hexane) to afford the desired product as a white solid
(0.38 g, 89%): TLC (10% MeOW90% CH202) Rf 0.04; 'H-NMR (DMSO-d6) 8 1.21 (s, 9H), 4.81 (s, 2H), 6.19 (s, IH), 7 7.35 (m, 2H), 8 8.12 (m, 1H), 8.76 (br
s, IH), 9.52 (br s, IH); FAB-MS m1z (rel abundance) 385 ((M+H)+, 100%).

Step 2. N-(]V-((Methylcarbamoyl)methyl) tert-butyl pyrazolyl)-N]-(2,3-dichlorophenyl)urea: A solution of N-(N'-(carboxymethyl) tert-butyl pyrazolyl)-N'-(2,3-dichlorophenyl)urea (100 mg, 0.26 mmole) and NN]-carbonyldiimidazole (45 mg, 0.28 mmole) in CH202 (10 mL) was stirred at room temp. 4 h at which time TLC indicated formation of the corresponding anhydride
(TLC (50% acetone/50% CH202) Rf 0.81). Dry methylamine hydrochloride (28 mg, 0.41 nunole) was then added followed by of diisopropylethylamine (0.07 mL, 0.40
mmole). The reaction mixture was stirred at room temp. overnight, then diluted with

CH202, washed with water (30 mL), a saturated NaCl solution (30 mL), dried (MgSO4) and concentrated under reduced pressure. The residue was purified by column chromatography (gradient from 10% acetone/90% CH202 to 40% acetone/60% CH202) and the residue was crystallized (Et2O/hexane) to afford the desired product (47 mg, 46%): TLC (60% acetone/40% CH202) Rf 0.59; 'H-NMR (DMSO-d6) 8 1.20 (s, 9H), 2.63 (d, J=4.5 Hz, 3H), 4.59 (s, 2H), 6.15 (s, IH), 7 7.34 (m. 2H), 8 8.12 (m, 2H), 8.79 (br s, 1H), 9.20 (br s, 1H); FAB-MS m1z (rel abundance) 398 ((M+H)+, 30%).

D5b. GeneraI Method for the Conversion of Ester-Containing Ureas into Arnide-Containing Ureas

0 0
N N)]N C02H
H H

Step 1. N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-carboxyphenyl)oxyphenyl)urea.

To a solution of N-(5-tert-butyl isoxazolyl)-N]-(4-(4-ethoxyoxycarbonylphenyl)-oxyphenyl)urea (0.524 g, 1.24 mmol) in a mixture of EtOH (4 ML) and THF (4 mL) was added a 1M NaOH solution (2 mL) and the resulting solution was allowed to stir overnight at room temp. The resulting mixture was diluted with water (20 mL) and treated with a 3M HO solution (20 mL) to form a white precipitate. The solids were lo washed with water (50 mL) and hexane (50 mL) , and then dried (approximately 0.4 mmHg) to afford the desired product (0.368 g, 75 %). This material was carried to the next step without further purification.

0 0
Zl]' I NHMe
N H H
N N
0

Step 2. N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-(N-methylcarbamoyl)-phenyl)oxyphenyl)urea: A solution of N-(5-tert-butyl isoxazolyl)-N-(4-(4-carboxyphenyl)oxyphenyl)urea (0.100 g, 0.25 mmol), methylamine (2.0 M in TBF; 0.140 mL, 0.278 mmol), I -ethyl (3-dimethylaminopropyl)carbodiimide hydrochloride (76 mg, 0.39 mmol), and N-methyhnorpholine (0.030 mL, 0.27 mmol) in a mixture of TBF (3 rnL) and DW (3mL) was allowed to stir overnight at room temp. then was poured into a IM citric acid solution (20 mL) and extracted with EtOAc (3 x 15 mL). The combined extracts were sequentially washed with water (3 x 10 mL) and a saturated NaCI solution (2 x 10 mL), dried (Na2SOA filtered, and concentrated in vacuo . The resulting crude oil was purified by flash chromatography (60 % EtOAc/40% hexane) to afford the desired product as a white solid (42 mg, 40%): EI-MS m1z 409 ((M+H)+).

D6. General Method for the Conversion of co-Amine-Containing Ureas into

Amide-Containing Ureas
0 0
N N)] N NH2
H H
N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-aminophenyl)oxyphenyl)urea: To a solution
of N-(5-tert-butyl isoxazolyl)-N]-(4-(4-tert-butoxycarbonylaminophenyl)oxy-
phenyl)-urea (prepared in a manner analogous to Methods B6 then C2b; 0.050 g,
0. 1 1
mmol) in anh 1,4-dioxane (3 mL) was added a conc HCI solution (1 mL) in one
portion and the mixture was allowed to stir overnight at room temp . The
mixture was
then poured into water (10 mL) and EtOAc(10 mL) and made basic using a 1M
lo NaOH solution (5 mL). The aqueous layer was extracted with EtOAc (3 x 10
mL).

The combined organic layers were sequentially washed with water (3 x 1 00 mL)
and a
saturated NaCl solution (2 x 100 mL), dried (Na2SO4), and concentrated in
vacuo to
afford the desired product as a white solid (26 mg, 66%). EI-MS mlz 367 ((M+
H)+).

D7, General Method for the Oxidation of Pyridine-Containing Ureas
0
N]
0
N N N'I::::D
H H
N-(5-tert-Butyl isoxazolyl)-N]-(4-(N-oxo4-pyridinyl)methylphenyl)urea: To a
solution of N-(5-tert-butyl isoxazolyl)-N]-(4-(4-pyridinyl)methylphenyl)urea
(0.100
g, 0.29 mmol) in CHC13 (10 mL) was added m-CPBA (70% pure, 0.155 g, 0.63
mmol) and the resulting solution was stirred at room temp for 16 h. The
reaction
mixture was then treated with a saturated K2CO3 solution (10 n1L). After 5
min, the
solution was diluted with CHC13 (50 mL). The organic layer was washed
successively with a saturated aqueous NaHS03 solution (25 mL), a saturated
NaHCO3
solution (25 mL) and a saturated NaCl solution (25 mL), dried (MgS04), and
concentrated in vacuo. The residual solid was purified by MPLC (15% MeOH/85%
EtOAc) to give the N-oxide (0.082 g, 79%).

D8. General Method for the Acylation of a Hydroxy-Containing Urea
0 0 0
N
N N
H H
N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-acetoxyphenyloxy)phenyl)urea: To a
solution of N-(5-tert-butyl isoxazolyl)-N-(4-(4-hydroxyphenyloxy)phenyl)urea
(0.100 g, 0.272 mmol), NN-dimethylaminopyridine (0.003 g, 0.027 mmol) and
Et3N
(0.075 mL, 0.544 mmol) in anh TBF (5 mL) was added acetic anhydride (0.028
mL,
0.299 mmol), and the resulting mixture was stirred at room temp. for 5 h. The
resulting mixture was concentrated under reduced pressure and the residue was
dissolved in EtOAc (10 mL). The resulting solution was sequentially washed
with a
5% citric acid solution (IO mL), a saturated NaHCO3 solution (1 0 mL) and a

saturated
NaCl solution (10 mL), dried (Na2S04), and concentrated under reduced pressure to
give an oil which slowly solidified to a glass (0.104 g, 93%) on standing under
reduced pressure (approximately 0.4 mmHg): TLC (40% EtOAc/60% hexane) Rf
0.55; FAB-MS m1z 410 ((M+H)+).

D9. Synthesis of (o-Alkoxypyridines
0 0
oo]
N N N N 0
H H H
Step 1. N-(5-tert-Butyl isoxazolyl)-N]-(4-(2(lH)-pyridinon yl)oxyphenyl)-urea: A solution of N-(5-tert-butyl isoxazolyl)-N-(4-(5-(2-methoxy)pyridyl)-oxyaniline (prepared in a manner analogous to that described in Methods B3k and
C3b; 1.2 g, 3.14 mmol) and trimethylsilyl. iodide (0.89 mL, 6.28 mmol) in CH202
(30 mL) was allowed to stir overnight at room temp., then was to 40 'C for 2 h. The
resulting mixture was concentrated under reduced pressure and the residue was purified by column chromatography (gradient from 80% EtOAc/20% hexans to 15% MeOH/85% EtOAc) to give the desired product (0.87 g, 75%): mp 175-180 'C; TLC (80% EtOAc/20% hexane) Rf 0.05; FAB-MS m1z 369 ((M+H)+5 100%).

N N Nj::r OEt
H H
Step 2. N-(5-tert-Butyl isoxazolyl)-N]-(4-(5-(2-Ethoxy)pyridyl)oxyphenyl)urea
.

A slurry of N-(5-tert-butyl isoxazolyl)-N-(4-(2(lH)-pyridinon yl)oxyphenyl)urea
(0. 1 g, 0.27 mmol) and A92CO3 (0.05 g, 0. I 8 mmol) in benzene (3 mL) was stirred at
room temp. for 10 min. Iodoethane (0.023 mL, 0.285 mmol) was added and the resulting mixture was heated at the reflux temp. in dark overnight. The reaction
mixture was allowed to cool to room temp., and was filtered through a plug of Celite OD
then concentrated under reduced pressure. The residue was purified by column chromatography (gradient from 25% EtOAc/75% hexane to 40% EtOAc/60% hexane) io to afford the desired product (0.041 g, 38%): mp 146 'C; TLC (40% EtOAc/60%
hexane) Rf 0.49; FAB-MS m1z 397 ((M+H)+] 100%).

D10, Reduction of an Aldehyde- or Ketone-Containing Urea to a Hydroxide-Containing Urea
0 0
N N)] NZr IDY
1 5 H H OH
N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-(l-hydroxyethyl)phenyl)oxyphenyl)urea.

To a solution of N-(5-tert-butyl isoxazolyl)-N]-(4-(4-(I-acetylphenyl)oxyphenyl)urea (prepared in a manner analogous to that described in
Methods B1 and C2b; 0.060 g, 0.15 mmol) in MeOH (10 mL) was added NaBH4
(0.008 g, 0.21 mmol) in one portion. The mixture was allowed to stir for 2 h at room
temp., then was concentrated in vacuo. Water (20 mL) and a 3M HCI solution (2

m.L)
were added and the resulting mixture was extracted with EtOAc (3 x 20 mL). The
combined organic layers were washed with water (3 x 10 mL) and a saturated NaCl
solution (2 x 1 0 mL), dried (MgSO4), and concentrated in vacuo . The resulting white
solid was purified by trituration (Et20/hexane) to afford the desired product (0.021 g, .
32 %): rnp 80-85 T; 1H NMR (DMSO-d6) 8 1.26 (s, 9H), 2.50 (s, 3H), 4.67 (m, 1H),
5.10 (br s, 1H), 6.45 (s, 1H), 6.90 (m, 4H), 7.29 (d, J- 0 Hz, 2H), 7.42 (d, J=9.0 Hz,
2H)q 8.76 (s, IH), 9.44 (s, 1H); HPLC ES-MS m1z 396 ((M+H)+).

D11. Synthesis of Nitrogen-Substituted Ureas by Curtius Rearrangement of Carboxy-Substituted Ureas
H
0 N 0 N]] Ph
0 Y
oe;:] 0
N N Nicr 101o]
H H
N-(5-tert-Butyl isoxazolyl)-N]-(4-(3-(benzyloxycarbonylamino)phenyl)-oxyphenyl)urea: To a solution of the N-(5-tert-butyl isoxazolyl)-N-(4-(3-carboxyphenyl)oxyphenyl)urea (prepared in a manner analogous to that described in
Methods B3a, Step 2 and C2b; 1.0 g, 2.5 mmol) in anh toluene (20 mL) was added
Et3N (0.395 mL, 2.8 mmol) and DPPA (0.610 mL, 2.8 mmol). The mixture was
io heated at 80 OC with stirring for 1.5 h then allowed to cool to room temp. Benzyl
alcohol (0.370 mL, 3.5 mmol) was added and the mixture was heated at 80 'C with
stirring for 3 h then allowed to cool to room temp. The resulting mixture was poured
into a 10% HO solution (50 mL) and teh resulting solution extracted with EtOAc (3 x
50 mL). The combined organic layers were washed with water (3 x 50 mL) and a saturated NaCl (2 x 50 mL), dried (Na2SO4), and concentrated in vacuo. The crude
oil was purified by column chromatography (30% EtOAc/70% hexane) to afford the
desired product as a white solid (0.7 g, 60 %): rnp 73-75 'C; 'H NMR (DMSO-d6) 8
1.26 (s, 9H), 5.10 (s, 2H), 6.46 (s, 1H), 6.55 (d, J=7.0 Hz, IH), 6.94 (d, J=7.0 Hz,
2H), 7.70 (m, 7H), 8.78 (s, 1H), 9.46 (s, 1H), 9.81 (s, 1H); BPLC ES-MS m1z 501
((M+H)+).

The following compounds have been synthesized according to the General Methods
listed above.

Table 1. 5-Substituted isoxazolyl Ureas
Ri
0
0 2
)] R

N N
H H
EX. R1 R' mp TLC Solvent Mass Synth.

(C) Rf System Spec. Source Method
I t-Bu F 169- 0.45 25% 357 FAB Clb
172 EtOAc / (M+H)+
75%
hexane
2 t-Bu Me Me 0.63 5% 288 FAB C2a
MeOH / (M+H)+
95%
CH2CI2
3 t-Bu 169- 424 FAB Qb] D2
Jr 0 OBu-n
f \.-/- _& 171 (M+H)+
4 t-Bu 0.19 50% 423 FAB C2bq D3
NH
]=O EtOAc (M+H)+
Et 50%
hexane
5 t-Bu 202- 0.15 60% 409 FAB C2b] D3
NH
/]=O 206 EtOAc (M+H)+
Me 40%
1 hexane
6 t-Bu 214- 0.75 60% 463 FAB Ub] D3
NH
]=O 217 EtOAc / (M+H)+
F3C 40%
hexane
7 t-Bu 0-&OBn 157 0.42 40% 458 FAB B3a,
EtOAc / (M+H)+ C2b
60%
hexane
8 t-Bu 148- 352 FAB CIC
149 (M+H)+
9 t-Bu Cl Cl 0.12 20% 329 BPLC/ CIC
EtOAc (M+H)+ ES-MS
80%
hexane
10 t-Bu Cl 176- 0.50 30% 400 (M+) BpLC/ C2b
177 EtOAc ES-MS
70%
hexane
I I t-Bu 156- 0.50 30% 366 BPLC/ C2b
157 EtOAc (M+H)+ ES-MS
70%
hexane
12 t-Bu 190- 0.15 30% 350 (M+) EI C2b
C! C\N 191 EtOAc
70%
hexane
t-Bu 175- 0.25 30% 409 HPLC/ DU
N 177 EtOAc (M+H)+ ES-MS Step I
O___], 1 70% B3b
S:0] hexane Step 2,
C2b
14 t-Bu 0 0.35 30% 402 HPLC/ B3bj
EtOAc (M+H)+ ES-MS C2b

```
70%
hexane
15 t-Bu 0.1 10% 350 HPLC/ C2b
MeOH (M+H)+ ES-MS
0 90%
CH202
16 t-Bu ___ao_C 15% 352 (M+) EI C2b
N 240- 0.2
243 MeOH /
85%
I EtOAc
17 t-Bu --&O-&OH 0.15 30% 367 (M+) EI B3a,
EtOAc / C2b, D2
70% Step 1
hexane
18 t-Bu S- C\N 178- 368 (M+) EI B4a,
I 179 1 1 C2b
19 t-Bu H2 N .25 30% 351 FAB Bl] C2b
CLoN 164- 0
165 EtOAc / (M+H)+
70%
hexane
20 t-Bu --- aH N 170- 0.15 30% 351 FAB B71 B12
c 172 EtOAc / (M+H)+ C2b
70%
hexane
21 t-Bu HO 0.3 25% 368 FAB C2b
0 EtOAc / (M+H)+
75%
hexane
22 t-Bu H2 188- 367 FAB D7
__&CLC\N-a,-o 191 (M+H)+
23 t-Bu Me 0.8 25% 366 FAB B3a,
EtOAc / (M+H)+ C2b
75%
hexane
24 t-Bu _JF]\O-&OMe 155- 0.55 30% 382 FAB B3a,
156 EtOAc / (M+H)+ C2b
70%
hexane
25 t-Bu 145- 0.6 25% 438 FAB B3a,
0
-&OArn-n 148 EtOAc / (M+H)+ C2b, D2
75%
hexane
26 t-Bu -1/-\\-o OPr-n 137- 0.62 25% 410 FAB B3a,
141 EtOAc / (M+H)+ C2bq D2
75%
hexane
t-Bu --//]\]O_&opr_j 164- 0.6 25% 410 FAB B3a,
166 EtOAc / (M+H)+ Ub] D2
75%
hexane
28 t-Bu --//---% &OBu-i 69- 0.6 25% 424 FAB B3a,
7 1 EtOAc / (M+H)+ MI D2
75%
hexane
29 t-Bu OH 78- 0.15 25% 368 FAB C2b
0 80 EtOAc (M+H)+
75%
```

hexane
30 t-Bu 0 235 0.35 25% 402 FAB Wb]
EtOAc (M+H)+ C2b
75%
hexane
3 1 t-Bu s 201- 0.35 25% 418 FAB B3bq
202 EtOAc (M+H)+ C2b
75%
hexane
32 t-Bu 158- 0.25 30% 369 FAB B4a,
159 EtOAc (M+H)+ C2b
S- C\N 70%
hexane
33 t-Bu CF3 180- 0.15 30% 437 FAB Wb]
._]]S_C 181 EtOAc / (M+H)+ C2b
N 70%
1 hexane
34 t-Bu N 68- 0.3 50% 370 FAB B4a,
s 71 EtOAc / (M+H)+ C2b
-a --O\/T
N 50%
hexane
35 t-Bu N 159- 0.2 50% 370 FAB B4a,
S.- C\- /) 161 EtOAc / (M+H)+ C2b
N 50%
1hexane
36 t-Bu S_.&C, 183. 0.3 30% 403 FAB C2b
186 EtOAc / (M+H)+
N 70%
hexane
37 t-Bu F3C 98- 0.25 10% 454 FAB C2b
cl 101 EtOAc / (M+H)+
90%
hexane
38 t-Bu 163- 0.25 20% 394 FAB B12 C2b
-ao 166 EtOAc / (M+H)+
80%
hexane
39 t-Bu O-&SMe 144- 0.3 30% 403 FAB C2b
147 EtOAc / (M+H)+
N
70%
hexane
40 t-Bu 0-&OMe 155- 0.25 10% 454 FAB C2b
157 EtOAc (M+H)+
N
90%
hexane
t-Bu 162- 0.25 20% 394 FAB B19 C2b
--&S-&F 164 EtOAc (M+H)+
80%
hexane
42 t-Bu S--&Me 149- 0.15 15% 3 FAB C2b
150 EtOAc (M+H)+
85%
hexane
43 t-Bu N 200- 0.35 50% 354 FAB Wj]
0 D/T
N 201 EtOAc / (M+H)+ C2b
50%

hexane
44 t-Bu 77- 0.3 30% 408 (M+) El B3e,
80 EtOAc / C2b
N
s 70%
hexane
45 t-Bu N 162- 0.17 40% 354 FAB B3jj
o - C /)
N 164 EtOAc (M+H)+ C2b
60%
hexane
46 t-Bu N 30% 368 (M+) El B29 C2b
73- 0.2
76 EtOAc
70%
hexane
47 t-Bu 185- 0.30 30% 413 FAB C2b
\---/--S-&NO2 188 EtOAc (M+H)+
70%
hexane
48 t-Bu S-&Pr-i 159- 410 FAB B29 C2b
160 (M+H)+ 1
49 t-Bu MeO 73- 0.15 25% 428 FAB B25C2b
s 75 EtOAc (M+H)+
--t] 75%
)Me hexane
50 t-Bu Me 188- 0.25 5% 422 FAB B1, C2b
0 - M e
190 EtOAc (M+H)+
Et 95%
hexane
5 1 t-Bu]\S--&OMe 143- 0.25 30% 398 FAB B3e,
145 EtOAc (M+H)+ C2b
70%
hexane
52 t-Bu s OMe 148- 0.25 30% 428 FAB B3e,
151 EtOAc (M+H)+ C2b
OMe 70%
hexane
53 t-Bu 0 - C\N 0.30 100% 353 FAB BO
I EtOAc (M+H)+ Ob
54 t-Bu 172- 0.25 10% 420 FAB C2b
-F\]-O-&CF3
174 EtOAc (M+H)+
90%
hexane
55 t-Bu o OMe 126- 0.25 30% 412 FAB B3e,
129 EtOAc (M+H)+ C2b
OMe 70%
hexane
t-Bu 0 201- 0.25 10% 396 FAB B3e,
-Q 204 EtOAc (M+H)+ C2bq D2
oEt 90%
hexane
57 t-Bu N 163- 0.30 40% 369 FAB B4a,
164 EtOAc (M+H)+ C2b
60%
hexane
58 t-Bu 162- 0.20 25% 363 (M+) El C2b
163 EtOAc

```
75%
hexane
59 t-Bu 0 N 127- 0.22 40% 353 FAB 133e
129 EtOAc (M+H)+ Step 1,
60% B29 C2b
hexane 1
60 t-Bu 85- 0.20 50% 402 (M+) El We
0 -
N 87 EtOAc / Step I 9
50% B21 C2b
hexane
61 t-Bu Meo 108- 0.25 10% 381 El 133e,
110 EtOAc / (M+H)+ C2b
90%
1hexane
62 t-Bu C02Et 153- 0.25 30% 424 FAB B3e,
- - 0 155 EtOAc / (M+H)+ C2b
70%
hexane
63 t-Bu ]\o NH 117- 0.25 10% 467 FAB B69 C2b
]=o 120 EtOAc / (M+H)+
t-BuO 90%
1 hexane
64 t-Bu 0 186- 0.25 30% 367 FAB 136]
NH2 189 EtOAc / (M+H)+ MI D6
70%
hexane
65 t-Bu 0 209- 0.25 60% 423 FAB B3e,
--/F
--\ ]/NW2 212 EtOAc (M+H)+ Qb]
40% D5b
hexane
66 t-Bu 0
221- 0.25 60% 409 FAB B3e,
k- ]/NHme 224 EtOAc (M+H)+ C2bq
40% D5b
hexane
67 t-Bu 0 Me 114- 0.25 60% 409 FAB B3e,
jr 0 117 EtOAc (M+H)+ Ub]
j 40% D5b
-A.-j d/-NH
Ihexane
68 t-Bu 0 201- 0.25 60% 423 FAB B3e,
]-NW2 203 EtOAc (M+H)+ C2b
40% D5b
hexane
69 t-Bu 145- 0.25 30% 423 (M+) El B3e,
&Co2Et
147 EtOAc C2b
70%
hexane
t-Bu --aO-&F 148- 0.25 20% 370 FAB B3e,
151 EtOAc / (M+H)+ C2b
80%
hexane
71 t-Bu 0 188- 0.25 20% 382 FAB B3e,
-Q 201 EtOAc / (M+H)+ C2b
OMe 80%
I hexane
72 t-Bu N 134- 0.25 20% 367 FAB B3e,
```

```
0- a\/ Me 136 EtOAc / (M+H)+ C2b
80%
hexane
73 t-Bu 152- 0.25 20% 396 FAB B3e,
0
--\OMe 155 EtOAc (M+H)+ C2b
80%
hexane
74 t-Bu 0-< 176- 0.25 50% 403 FAB B3e,
178 EtOAc (M+H)+ C2b
N
,T-]]
N- 50%
hexane
75 t-Bu 200 0.30 5% 396 FAB B3a
]0--&CO,H
dec MeOH (M+H)+ Step 2,
0.5% C2b
AcOH
94.5%
CH202
76 t-Bu 0 177- 419 FAB B89
2 180 (M+H)+ Wb]
C N] 10
C2b
0
77 t-Bu - 0.60 60% 485 FAB C2b, D3
NH
>=O EtOAc (M+H)+
CH2 40%
0 hexane
78 t-Bu Et 194- 0.24 5% 377 FAB Oa
N 195 MeOH (M+H)+
95%
CH2C12
79 t-Bu H 160- 0.79 75% 381 FAB C3a
-C\\]41-&OMe
162 EtOAc (M+H)+
25%
hexane
80 t-Bu
140- 0.25 50% 352 (M+) El B4b]
143 EtOAc Ob
0-% N 50%
I CH2Cl2
81 t-Bu 147- 0.25 50% 352 (M+) El Wf]
-Q 150 EtOAc Ob
0- 50%
N C11202
82 t-Bu 166- 0.44 50% 396 FAB Ob
o 0 170 EtOAc (M+H)+
0 50%
hexane
t-Bu 175- 0.05 80% 369 FAB B3
_Q 180 EtOAc / (M+H)+ C3bq D9
0 :\'-o 20%
- C\NH hexane
84 t-Bu 190- 0.25 50% 367 FAB B3g,
_Q N 193 EtOAc / (M+H)+ C3b
0 - &\'/' Me 50%
```

```
I CH2C12
85 t-Bu Me 136- 0.25 50% 367 FAB 134b,
140 EtOAc (M+H)+ C3b
0 - (\]N 50%
CH202
8 6 t-Bu Me 65- 0.25 50% 367 FAB B4b2
67 EtOAc (M+H)+ C3b
50%
1 CH202
87 t-Bu Me 68- 0.25 50% 383 FAB 134a,
--&S-- C\N 72 EtOAc (M+H)+ C3b
50%
CH2C12
88 t-Bu N 146 0.49 40% 397 FAB 133k]
0 - a\/ OEt EtOAc (M+H)+ C3bj D9
60%
hexane
89 t-Bu N 100 0.54 40% 411 FAB BR,
0 - C\:I
]-OPrn EtOAc (M+H)+ C3bq D9
60%
hexane
90 f-Bu 0 N 100 0.62 40% 411 FAB BR7
,\_ -- -&' -i
Opr EtOAc / (M+H)+ 0b] D9
60%
hexane
9 1 t-Bu Me 164- 0.25 50% 382 (M+) El 134a,
165 EtOAc / C3b
S-]\]N 50%
CH2C12
92 t-Bu - H2 175- 0.25 20% 485 FAB B3e,
\\,*-C-NH 177 EtOAc (M+H)+ C3bq
0 80% D5b
hexane
93 t-Bu 0 94- 0.25 20% 390 FAB B59 C3b
97 EtOAc (M+H)+
80%
OEt hexane
94 t-Bu H I T 0.30 50% (M+) El C3a, D2
\\]NI _aOH
141 EtOAc step 1
50%
hexane
95 t-Bu OH 0.15 100% 367 FAB B9, Ch
]\N EtOAc (M+H)+
96 t-Bu NH 120- 0.25 20% 471 HPLC 133e,
122 EtOA
0 c/ (M+H)+ ES-MS C3bj
80% D5b
hexane
t-Bu Et-NH 168- 0.25 50% 423 HPLC B3e,
0 170 EtOAc (M+H)+ ES-MS C3bj
50% D5b
hexane
98 t-Bu OH 80- 0.25 50% 396 HPLC BI,
85 EtOAc (M+H)+ ES-MS Qb]
50% DIO
hexane
99 t-Bu 0 73- 0.25 30% 501 HPLC B3a
```

04 75 EtOAc (M+H)+ ES-MS step 2,
NH 70% Ub]
hexane DIl
100 t-Bu Br 240] 414. 414 HPLC
DEC 95 (M+H)+ ES-MS
3r
101 t-Bu O OH 132- 0.52 40% 383 FAB B3a,
134 EtOAc (M+H)+ BIq C3b
60%
hexane
103 t-Bu 0 0.52 100% 396 HPLC B109
]-NH2 EtOAc (M+H)+ / ES- B4bj
__/T]\O-]\]N MS C2b
104 t-Bu 0 107- 0.85 100% 410 FAB B10,
_Q NHMe 110 EtOAc (M+H)+ B4bq
O-< N C2b
105 t-Bu 0 0.75 100% 396 HPLC B10,
NH2 EtOAc (M+H)+ / ES- B02
_Q - MS C2b
O-< N
106 t-Bu 0 132- B3d
142 135 step 2,
C3a
107 t-Bu 0.45 100% 369 FAB C2b
EtOAc (M+H)+
108 t-Bu 0.60 100% 365 FAB C2b
EtOAc (M+H)+
109 t-Bu O 0.55 40% 410 FAB B3bj
]=O EtOAc (M+H)+ C2bq D2
me 60% Step 1,
hexane D8
110 t-Bu 176- B7. C2a
N 178
&2 CH2
III i-Bu __/F]\ 195- 0.30 25% 397 FAB C2b
aNO2 197 EtOAc (M+)
75%
hexane
112 t-Bu N 179- B3b2
182 C2a
t-Bu Me 78- 0.25 10% 379 EI We,
82
EtOAc (M+) Ob
90%
Me CH2CI2
114 t-Bu H2 203- 0.35 10% 340 FAB B89
206 MeOH (M+H)+ B2bq
0.5% C2b
AcOH
89.5%
EtOAc
115 t-Bu H 189- 0.20 30% 351 FAB C2b
191
EtOAc (M+H)+
70%
hexane
116 t-Bu F 0.60 5% 404 FAB B3b
acetone (M+H)+ step 1,2,
95% Cld
CH2CI2

117 t-Bu 0 234 0.30 5% 396 FAB B3a
OH dec MeOH/ (M+H)+ Step 2,
0 0.5% C2b
AcOH
94.5%
CH202
118 t-Bu 0 135-
\---/]D 138
119 t-Bu --Q 0 0.13 5% 486 FAB B3b
acetone (M+H)+ step 1,2,
Cl 95% Cld
CH202
121 t-Bu 177- 0.20 30% 351 FAB B7] B19
-Q 178 EtOAc / (M+H)+ C2b
H 2 C 70%
I hexane
122 t-Bu O - P]\-Jj 0.40 25% 366 FAB B3a,
EtOAc / (M+H)+ C2b
Me 75%
hexane
123 t-Bu 0 Me 150- 0.45 25% 380 FAB B3a,
158 EtOAc / (M+H)+ C2b
Me 75%
hexane
124 t-Bu 0 Cl 118- 0.50 25% 420 FAB B3a
122 EtOAc / (M+H)+ Step I
Cl 75% B3b
hexane Step 2,
C2b
125 t-Bu -ao-Q 176- 0.55 25% 366 FAB B3a,
182 EtOAc / (M+H)+ C2b
Me 75%
hexane
126 t-Bu 176- 0.16 5% 386 FAB C2b
177 MeOH / (M+H)+
95%
CH202
Table 2. 3-Substituted isoxazolyl Ureas
R'
,]Yj 0
N I)] R2
0 N N'
H H
mp TLC Solvent Mass Synth.

Ex. R1 R2 ('C) Rr System Source Method
IN
137 Me 0--aMe 169- 0.25 5% 324 FAB Clb
170 acetone /(M+H)+
95%
CH2CI2
138 i-Pr --&O-aMe 166- 0.54 50% 352 FAB Clb
170 EtOAc (M+H)+
50% pet
ether
139 i-Pr Cl Cl 148- 0.40 5% 313 El Clb
149 acetone /(M+)
95%
CH2C12
i-Pr H2 272 0.21 5% 337 FAB A2, C3a

```
--a CL C\N dec MeOH (M+H)+
95%
CHC13
141 i-Pr 0.25 5% 355 FAB A2]
_Q MeOH (M+H)+ B4a,
S - ]\:N 95% C3a
CHC13 I
142 i-Pr OMe 0.14 30% 368 FAB A21
EtOAc (M+H)+ B3a,
70% pet C3a
ether
143 i-Pr -a 0 - C\N 75- 0.22 5% 339 FAB A2, C3a
77 MeOH (M+H)+
dec 95%
1 CH202
144 i-Pr -&S- C\N 112- 0.29 5% 355 FAB A21
117 MeOH (M+H)+ B4a,
95% C3a
CH202
145 Cl Cl 171 0.33 5% 326 FAB Clb
acetone (M+H)+
95%
CH2Cl2
146 0 -<\:N 351 HPLC C8
(M+H) / ES-
+ Ms
147 0.03 50% 401 FAB C8
0 -N
EtOAc (M+H)
50% +
hexane
148 0 159- 0.22 5% 325 HPLC C4a
160 EtOAc/ (M+H) ES-
95% + Ms
hexane
149 190- 0.38 50% 350 FAB Clb
191 EtOAc (M+H)+
Me 50% pet
ether
150 Me 175- 0.43 50% 364 FAB Clb
4> 178 EtOAc (M+H+)
Me 50% pet
ether
151 n-Bu Cl Cl 133 0.37 5% 328 FAB Clb
acetone / (M+H)+
95%
CH202
152 t-Bu --&O--aMe 165 0.34 40% 366 FAB Clb
dec EtOAc (M+H+)
60% pet
ether
153 t-Bu Br 188- 0.82 5% 338 FAB Clb
189 acetone (M+H)+
95%
CH2CI2
154 t-Bu 182- 352 FAB
184 (M+H)+
t-Bu Ci 0.65 5% 294 FAB C2a
MeOH (M+H)+
95%
```

CH202
156 t-Bu CF3 0.25 3% 328 FAB C2a
MeOH (M+H)+
97%
CH202
157 t-Bu Ci Ci 0.57 3% 328 FAB C2a
MeOll (M+H)+
97%
CH2CI2
158 t-Bu 0.60 5% 274 FAB C2a
--Me
MeOll (M+H)+
95%
CH2CI2
159 t-Bu --&S- C\N 0.21 5% 369 FAB 134a,
MeOH (M+H)+ C2a
95%
Cli2CI2
160 t-Bu --/F]\S-a0l`r-n 0.52 50% 426 FAB B5, C4a
EtOAc / (M+H)+
50%
hexane
161 t-Bu --&O--&OBn 0.36 40% 458 FAB 133a,
EtOAc / (M+H)+ C2b
60%
hexane
162 t-Bu 213 0.05 5% 369 FAB C3a
dec acetone / (M+H)+
S- C\N 95%
1 CH2C12
163 t-Bu --& 0 - C\N 210 0.05 5% 353 FAB C3a
dec acetone / (M+H)+
95%
CH202
164 t-Bu 174- 0.25 5% 382 FAB C3a
O-aOMe
175 acetone / (M+H)+
95%
CH202
165 t-Bu 90- 0.16 5% 409 FAB C2a
N 92 acetone / (M+H)+
0--], 1 95%
S:04 CH2C12
166 t-Bu N 221 0.14 5% 409 FAB C2a
0--\0] 10
s , 1]0 dec acetone (M+H)+
95%
CI-I2Cl2
167 t-Bu H 182 0.28 40% 380 El A2, C3a
-F\]-N OMe EtOAc (M+)
60%
hexane
168 t-Bu N 196- 0.17 5% 368 FAB A21
-IN
0 -]\]/ OMe
198 MeOll (M+H)+ B314
N 95% C3a
I I CH2C12
t.-Bu 0-&OMe 204- 0.27 50% 383 FAB A2]
-&N 206 EtOAc (M+H)+ B3a,

```
50% pet C3a
ether
170 t-Bu
---/ \\-H2 179- 351 FAB A2, C3a
--\=/-C-]\ N 180
(M+H)+
171 t-Bu 0.33 50% 414 EI A21
-&s--&SMe EtOAc (M+) B4a,
N
50% pet C3a
ether
172 t-Bu \N 0-&SMe 188- 0.49 50% 399 HPLC A29
189 EtOAc (M+H)+ ES- B4a,
N
50% pet Ms C3a
ether
173 t-Bu 0
179. 0.14 5% 395 FAB A25
Me 180 MeOH (M+H)+ B4a,
95% C3a
CH2CI2
174 t-Bu 0-&F 118- 0.19 5% 387 FAB A29
121 MeOH (M+H)+ B4a,
N
95% C3a
CH2Cl2
175 t-Bu 0 N 197- 0.08 10% 353 FAB All
199 acetone (M+H)+ B3h,
90% C3a
CH2CI2
176 t-Bu 208- 0.17 5% 3 FT FAB Ob
212 MeOH (M+H)+
95%
CH2CI2
177 t-Bu S--&OCF3 155- 0.57 10% 453 FAB Ob
156 MeOH / (M+H)+
CH2CI2
178 t-Bu \N 0-&SCF3 163- 0.21 5% 453 BPLC Ob
165 MeOH (M+H)+ / ES-
95% Ms
CH2CI2
179 t-Bu 109- 0.17 5% 369 FAB Ob
112 MeOH (M+H)+
95%
CH2CI2
180 t-Bu N02 199- 0.60 5% Ob
202 MeOH
I -&-O I CH202
181 t-Bu 160- 0.58 50% 336 Cl Ob
162 EtOAc (M+)
50% pet
ether
182 t-Bu
--// \ S-&OMe 0.18 50% Ob
\c4- EtOAc
50% pet
ther
183 t-Bu 180 Ob
/ \N O-ame
-CY
```

```
N
184 t-Bu 0 214- Ob
-& 217
N Cl
-C -
N
t-Bu N 0.13 50% 337 Ci Ob
EtOAc (M+H)
50% +
hexane
186 t-Bu 154- 0.51 50% 336 FAB Ob
156 EtOAc (M+H)
50% pet +
ether
187 Me 154- 0.50 50% 365 El Cib
-.]-Me -ao-o 155 EtOAc (M+)
Et 50% pet
ther
188 Me 25- 0.05 5% 383 FAB Oa
---],Me 221 acetone (M+H)+
Et
S -<\:N dec 95%
1 CH202
189 Me 137- 0.25 5% 396 FAB C3a
---\,]-Me -a OMe 138 acetone (M+H)+
Et 95%
CH202
190 Me Ci Ci 196- 0.58 5% 342 FAB Clb
--]-Me 199 acetone / (M+H+)
Et 95%
CH202
19.1 Me Me 0-&Me 160- 0.37 5% 380 FAB Clb
-a 162 acetone / (M+H+)
Et 95%
CH202
192 Me N 199- 0.33 70% 468 FAB A29
--\]-me --ao--/\, S:010:] 200 EtOAc (M+)+ 133e,
Et 30% pet Oa
ether
193 Me H 161- 0.28 40% 394 El A2, E3a
--]-Me -aN-aOMe 162 EtOAc (M+)
Et 60%
hexane
194 Me H2 0.18 5% 364 El A2, Oa
]- Me C - ]\]N MeOH (M+)
Et 95%
CHC13
195 Me 90- 0.19 30% 232 El A2, C3a
-\]-Me -a 0 - C\N 92 EtOAc (M+)
Et 70% pet
ether
196 Me 180- 0.26 30% A21
Me --ao-acl 181 EtOAc Ob
Et 70% pet
ether
197 Me 63- 410 FAB A2]
0-&OMe
65 (M+H)+ 133a,
Et Oa
198 Me 84 0.16 5% 381 FAB A2, Oa
```

---]-Me --&O-<\:N MeOH / (M+H)+
Et 95%
CHC13
199 Me 189- 0.16 5% 397 BPLC A21
--]-Et -aS- C\N 192 MeOH / (M+H)+ El-MS B4a,
Et 95% Oa
CHC13
Me H A2, C3a
CLC 175. 0.16 5% 379 FAB
]-Et N 177 MeOH (M+H)+
Et 95%
CHC13
201 Me 189- 0.17 5% 397 FAB A29
Et 191 MeOH (M+H)+ B4a,
Et -Q
S -- C\N 95% C3a
CHC13
202 Me 67 0.41 5% A25
-],Et -aO--&Me MeOH Ob
Et 95%
CHC13
203 Me 123- 414 FAB A2, C3a
--]-Et --&o-&ci 125 (M+H)+
Et I I 1
204 Me 135- 0.33 5% A25
--I;rEt 137 MeOH Ob
Et 95%
CHC13
205 Me 178- 0.39 5% 366 FAB Clb
-)7 180 acetone (M+H+)
Me Me
95%
CH2C12
206 --]-Me --&O-aMe 200- 0.44 5% 380 FAB Clb
202 acetone (M+H)+
Me Me
95%
CH2C12
207 Cl Cl 150- 0.39 5% 342 FAB Clb
rme
Me Me 154 acetone / (M+H)+
95%
CH202
208 155- 0.38 50% 377 EI Clb
156 EtOAc (M+)
50% pet
ether
209 Ph --aO-&Me 0.33 5% 386 FAB Clb
acetone (M+H)+
95%
CH202
210 s --&S- C\N 190- 0.23 5% 395 FAB A22
191 MeOH (M+H)+ B4a,
95% C3a
CH202
211 0 -aS- C\N 0.18 5% 379 FAB A21
MeOH (M+H)+ Ob
95%
CHC13
Table 3. N'-Substituted tert-butyl pyrazolyI Ureas

```
0
N% )] , R2
N N
H H
mp TLC Solvent Mass Synth.

Ex. R1 R] (OC) Rr System Spec. Source Method
212 H 0.27 50% 351 FAB Clc
EtOAc / (M+H)+
50%
hexane
213 H Cl Cl 0.59 50% 327 FAB CIC
EtOAc / (M+H)+
50%
hexane
214 H H2 0.30 60% 350 FAB C4a
-a CL C\N acetone (M+H)+
/40%
C112CI2
215 H --&O-&Me 204 0.06 5% 364 El C3b
acetone (M+)
/ 95%
CH2CI2
216 H 110- 0.05 5% 408 FAB C3b
N ill acetone (M+H+)
95%
S, ICH2C12
217 H 0 - C\N 228- 0.24 10% 351 El C3a
232 MeOH (M+)
dec 90%
CHC13
218 H Cl 182- 0.05 40% 327 FAB A53
C1 184 EtOAc (M+H)+ Cle
60%
hexane
219 H 110- 326 El A51
-0]-CF3 112 (M+) Cle
220 H 0.07 5% 368 FAB 134a,
MeOH / (M+H)+ C4a
S- C\N 95%
1 CHC13
221 H --O]S-- C\N 0.18 5% 364 EI B4,
MeOH / (M+) C4a
95%
CHC13
222 H 0 160- 408 FAB A59 B6,
.fl] 0 161 (M+H)+ C3b
HO CF3 NHMe isolated
at TFA
01 I salt
H --aO--&OMe 381 FAB C2b
L 1183] (M+H)+ I I
Me 0.35 70% 382 FAB B4a,
-&S- C\N acetone (M+H)+ C4a
/30%
CH202
225 Me 0.46 70% 382 FAB C4a,
acetone (M+H)+ B4a
S- C\N /30%
CH2Cl2
```

```
226 Me S]fS 0.47 100% 497 FAB B3c,
S-41 EtOAc (M+H)+ C4a
N-N 'Ph
227 Me s 0.46 100% 464 FAB B3c,
--]' I Ph EtOAc (M+H)+ C4a
I N I 1
228 Me S Ph 0.50 100% 540 FAB BR,
0](Ph
]\ EtOAc (M+H)+ C4a
229 Me CF3 0.52 100% 506 FAB BR,
N:O,
I EtOAc (M+H)+ C4a
s
230 Me CF3 0.51 100% 509 FAB BR,
-]] 0-&Ph EtOAc (M+H)+ C4a
231 Me 0-&Bu-t 0.75 100% 421 FAB BR,
-a EtOAc (M+H)+ C4a
232 Me O-aSCF3 0.50 100% 465 FAB BR,
EtOAc (M+H)+ C4a
233 Me Ph 0.50 100% 349 FAB C4a
EtOAc (M+H)+
234 Me 0.09 50% 381 FAB C4a
EtOAc (M+H)+
50%
hexane
235 Me 0-aOBn 0.60 100% 471 FAB B21
I IEtOAc (M+H)+ C4a
236 Me OH 0.61 100% 397 FAB BR,
-&S-a I EtOAc (M+H)+ C4a
237 Me S--&OPr-n 0.42 100% 439 FAB B5]
EtOAc (M+H)+ C4a
238 Me S--&OBu-n 0.25 50% 453 FAB B5]
EtOAc (M+H)+ C4a
50%
hexane
239 Me H2 0.65 100% 462 FAB B69
NH EtOAc (M+H)+ C4a
]=O
i-Bu
240 Me H2 0.67 100% 478 FAB B6]
C NH EtOAc (M+H)+ C4a
]=o
t-BuO
241 Me H2 0.50 1100%c 1378 FAB C4a
I I -0]- CL&-2 EtOA (M+H)+ I I I
Me H 0.30 100% 557 FAB C4a
NH EtOAc (M+H)+
]=O
RNe
243 Me H2 0.33 100% 420 FAB C4a,
C NH EtOAc (M+H)+ D3
/)==o
Me
244 Me H2 0.60 10% 478 FAB C4a,
NH water (M+H)+ D3
0 90%
H02C CH3CN
245 Me -4]VO-&]-/, NH 0.28 100% 559 FAB C4a
]=O EtOAc (M+H)+
HNe
```

246 Me -//]\\-O NH 0.40 100% 436 FAB C4a,
&-/N/]=O EtOAc (M+H)+ D3
Et/
247 Me NH 0.46 50% 422 FAB C4a,
]=O acetone (M+H)+ D3
Me 150%
CH2CI2
248 Me 0.50 100% 464 FAB C4a,
0 - NH EtOAc (M+H)+ D3
]=O
i-Bu
Me HL& 0.55 100% 434 FAB C4a,
249 2]-/
C NH EtOAc (M+H)+ D3
Et I 1
250 Me 0-aNH2 0.52 100% 380 FAB C4a
-a EtOAc (M+H)+
251 Me FAB C4a
\\-O-C\N 0.25 60% 366
acetone (M+H)+
/40%
CH2C12
252 Me 0.52 100% 452 FAB C4a,
-aO-<\a/N, NH EtOAc (M+H)+ D3
]=O
EtO
253 Me 0.52 100% 466 FAB C4a,
-aO- NH EtOAc (M+H)+ D3
]=O
i-pro
254 Me H2]- 0.34 60% 396 FAB C4a
-&S-C-]\]N acetone (M+H)+
/40%
CH2CI2
255 Me H2 0.36 60% 396 FAB C4a
--ac-S- C\N acetone (M+H)+
/40%
CH202
256 Me 0-0 147- 365 FAB CIC
I -]a 149 (M+H)+
257 Me Cl Cl 173- 341 FAB Clc
175 (M+H)+
Me CF3 185- 341 BIPLC / C I c
187 (M+H)+ ES-MS
259 Me Br 195- 429 FAB Clc
197 (M+H)+
Br
260 Me -.&CO2Bu-n 0.25 50% 373 FAB Clc
EtOAc / (M+H)+
50%
hexane
261 Me H2 161- 0.15 4% 364 FAB C2b
C I C\N 162 MeOH / (M+H)+
96%
CH2C12
262 Me '-&O-&Me 228 379 FAB C2b
dec (M+H)+
263 Me
0.30 5% 422 FAB C2b
MeOH / (M+H)+

N]
0__] - 95%
SAJ CH2CI2
264 Me CF3 0.32 70% 450 FAB Wb]
-]]S- C\N acetone (M+H)+ C4a
/30%
1 CH202
265 Me H2H2 0.15 40% 379 FAB B1] B2]
C - C acetone (M+H)+ Oa
N 60%
CH202
266 Me H2 0.10 20% 380 FAB C4a
--&O-CL C\N acetone (M+H)+
/ 80%
CH202
267 Me H 0.20 80% 365 FAB Oa
-F\\]-N- C\N
EtOAc / (M+H)+
20%
hexane
268 Me H2H2 r---\ 0.48 30% 378 FAB B11
acetone (M+H)+ C3a
/70%
CH2CI2
269 -CH2CF3 0.22 30% 433 FAB A3]
EtOAc (M+H)+ C1b
70%
hexane
270 -CH2CF3 Cl 1 0.38 30% 409 FAB A3]
EtOAc (M+H)+ C1b
./70%
hexane
271 -(CH2)2CN Cl Cl 0.53 70% 380 BPLC / A3,
EtOAc (M+) ES-MS C1b
30%
hexane
272 -(CH2)2CN 0.37 70% 404 BIPLC / A39
EtOAc (M+H)+ ES-MS Cib
30%
hexane
-(CH2)20H Cl Cl 0.15 60% 371 FAB A32
EtOAc / (M+H)+ CM
40% D4
hexane
274 --O 2 0.49 40% 432 FAB A31
C' C\N acetone (M+H)+ C4a
/ 60%
CH2CI2
275 -CH2CO2Et Cl Cl 0.44 50% 413 FAB A3]
EtOAc / (M+H)+ C1b
50%
hexane
276 Cl Cl 0.59 60% 398 FAB A3]
O=< CH2 acetone (M+H)+ C1b?
NHMe /40%. D5a
CH202
277 0 Me-NH 159- 508 FAB A59 B62
0 0 161 (M+H)+ C2b
t-B']
Table 4. 5-Substituted thiadiazolyl Ureas

RI
]-S O
N
'N N A W R2
H H
MP TLC Solvent Mass Synth.

Ex. R1 R] (OC) Rr System Spec. Source Method
278 t-Bu Me 243- 355 HPLC / Cic
JD 244 (M+H)+ ES-MS
279 t-Bu --&O--]&Me 0.30 5% 383 FAB Clb
acetone (M+H)+
/ 95%
C11202
280 t-Bu 0- C\N 0.26 5% 370 FAB C3a
MeOH / (M+H)+
95%
C11202
281 t-Bu 386 FAB 134a,
(M+H)+ C3a
S- C\N I 1
282 t-Bu --&O-&OMe 0.37 5% 399 FAB B3a,
MeOH / (M+H)+ C3a
95%
CH2C12
Table 5. 5-Substituted thienyl Ureas
RI
0
S])] , R2
N N
H H
2 mp TLC Solvent Mass Synth.

Ex. R1 R (OC) System Spec. Source Method
283 t-Bu 144- 0.68 5% A09
145 acetone Cla
/95%
C11202
284 t-Bu 0 N 0.28 50% 368 BPLC / A4a
Et2O (M+H)+ ES-MS
50% pet
ether
285 t-Bu e 57 381 FAB A4a
-ao-&M (M+H)+
286 t-Bu H2 0.15 50% 365 El A4a
--a C L C\N EtOAc / (M+)
50% pet
ether
287 i-Bu --&O-&OH 0.44 50% 383 FAB A4a
EtOAc / (M+H)+
50% pet
ether
t-Bu S- C\N 0.36 50% 384 FAB A4a
EtOAc / (M+H)+
50% pet
ether
289 t-Bu Cl Cl 169- 0.57 20% 343 FAB A4c,
170 EtOAc / (M+H)+ CId
80%
hexane

290 t-Bu 155- 0.40 20% 411 FAB D2
156 EtOAc / (M+H)+
80%
hexane
291 t-Bu O-aopr-i 165- 0.40 20% 425 FAB D2
166 EtOAc (M+H)+
80%
hexane
292 t-Bu _//]\]O-aOBu-i 188- 0.45 20% 439 FAB D2
189 EtOAc (M+H)+
80%
hexane
293 t-Bu 0 <\:N 0.13 50% 368 FAB A4c,
EtOAc (M+H)+ C4c
50%
hexane
294 t-Bu --&O-aOMe 0.26 30% 397 BPLC / A4c,
Et2O (M+H)+ ES-MS CId
70% pet
ether
295 t-Bu Me 0.52 30% 381 HPLC / A4a
Et2O (M+H)+ ES-MS
70% pet
ether
Table 5. Additional Ureas
mp TLC Solvent Mass Synth.

Ex. R' (OC) Rr System Spec. Source Method
296 161- 0.71 20% 367 FAB DI
163 EtOAc (M+H)+
0 80%
N]k NqC1 hexane
Br H H C1
297 162- 0.52 30% 365 FAB A89 Cld
0 164 EtOAc (M+H)
N 0 70% +
N)] Nia Me hexane
H H
298 Br 0.67 5% 388 FAB Clb
acetone (M+H)+
/95%
CH2CI2
N 0 f
N 'J] N
H H
C1 0.72 90% 380 BPLC MS
EtOAc / (M+H) ES
0 10% + B0]
HNI N hexane C4a
I
N N N
HH
300 170- 0.40 5% 328 FAB CM
172 acetone (M+H)+
/ 95%
N] CH202
0 NN C1
HH C1
301 179- 362 BPLC C5
181 (M+H)+ ES-MS

N 0
N)]N
H
302 155- 0.44 5% 380 FAB Clb
157 acetone (M+H+)
/ 95%
0 ON CH2CI2
NN']]
302 0.55 90% 443 FAB B101
0 EtOAc (M+H)+ B4b,
0 1 10% C2b
]U' zz]' N hexane
NNj:](
HH
NHMe
303 0 OEt 230 377 HPLC / C5
0 dec (M+H)+ ES-MS
NANjcc:p
H
BIOLOGICAL EXAMPLES
P38 Kinase AssM.

The in vitro inhibitory properties of compounds were determined using a p38 kinase
inhibition assay. P38 activity was detected using an in vitro kinase assay run in 96-
well microtiter plates. Recombinant human p38 (0.5 Vg/mL) was mixed with substrate
(myelin basic protein, 5 Vg/mL) in kinase buffer (25 mM Hepes, 20 mM M902 and
150 mM NaCI) and compound. One VCi/well of 33 P-labeled ATP (10 VW was added
io to a final volume of 100 VL. The reaction was run at 32 'C for 30 min. and stopped
with a IM HCl solution. The amount of radioactivity incorporated into the substrate
was detennined by trapping the labeled substrate onto negatively charged glass fiber
filter paper using a 1% phosphoric acid solution and read with a scintillation counter.

Negative controls include substrate plus ATP alone.

All compounds exemplified displayed p38 IC50S of between 1 nM and 10 jiM.

LPS Induced TNF Production in Mice.

The in vivo inhibitory properties of selected compounds were detennined using a
murine LPS induced TNFa production in vivo model. BALB/c mice (Charles River
Breeding Laboratories; Kingston, NY) in groups of ten were treated with either
vehicle or compound by the route noted. After one hour, endotoxin (E. coli
lipopolysaccharide (LPS) 100 4g was administered intraperitoneally (i.p.). After 90
io min, animals were euthanized by carbon dioxide asphyxiation and plasma was
obtained from individual animals by cardiac puncture ionto heparinized tubes. The
samples were clarified by centrifugation at 12,500 x g for 5 min at 4 'C. The
supernatants were decanted to new tubes, which were stored as needed at -20 'C.

TNFa levels in sera were measured using a commercial murine TNF ELISA kit (Genzyme).

The preceeding examples can be repeated with similar success by substituting the generically of specifically described reactants and/or operating conditions of this invention for those used in the preceeding examples From the foregoing discussion, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

CLAIMS (ENGLISH) What is claimed is:

1. A method for the treatment of a disease mediated by p38 other than cancer, comprising administering a compound of formula I

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wherein B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein if B is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and Xn, wherein n is 0-3 and each X is independently selected from the group consisting of -CN, -CO2R, -C(O)NRR5', -C(O)R, -NO2. -OR'q - SR5, - NRV, -NR'C(O)OR, -NR'C(O)R5', CI-Clo alkyl, C2-CIO alkenyl, CI-Clo alkoxy, C3-CIO cycloalkyl, C6-CI4 aryl, C7-C24 alkaryl, C3-CI3 heteroaryl, C4-C23 alkheteroaryl, substituted CI-CI(alkyl, substituted C2-Clo alkenyl, substituted CI-Clo alkoxy, substituted C3-CIO cycloalkyl, substituted C4-C23 alkheteroaryl and -Y-Ar; wherein if X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of -4CN, -COA5i -C(O)R', -C(O)NIeR, -OR5, -SR, -NRR. -NO2, -NRC(O)R, -NRC(O)OR and halogen up to per-halosubstitution; wherein R5 and W'are independently selected from H, CI-CIO alkyl, C2-CIO alkoyl, C3-CIO cycloalkyl, C6-CI4 arYl. C3-CI3 heteroaryl, C7-C24 alkaryl, C4-C23 3o alkheteroaryl, up to per-halosubstituted CI-Clo alkyl, up to per-halosubstituted C3-CIO cycloalkyl, up to per-halosubstituted C2-CIO alkenyl, up to per-halosubstituted C6-CI4 aryl and up to per-halosubstituted C3-CI3 heteroaryl, wherein Y is , -S-, -N(R)-g -(CH2)-m2 -C(O)-2 -CH(OH)-j -(CH2)mO-i -(CH2)mS-] -(CH2)mN(R)-i -O(CH2)m-i]CjjXa. NR5C(O)NR5 R5'_, _NR5C(O)_, -C(O)NR'-, -CXa2-, -S-(CH2),,,- and -N(R)(CH2)m-] m = 1-3, and V is halogen; and Ar is a 5-10 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z,,,, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of --CN, -CO2R, -C(O)NWR, -C(O)- NW9 -NOZ =07 -OR'q - SR']

NR'R. -C(O)R', -SO2R, -SO2NR'R, -NR'C(O)OR5'. -NR'C(O)W', CI-Clo alkyll
CI-Clo alkoxy, C3-CIO cycloalkyl, C6-CI4 aryl, C3-CI3 heteroaryl, C7-C24
alkaryl, C4-
C23 alkheteroaryl, substituted CI-CIO alkyl, substituted C3-CIO cycloalkyl,
substituted
C7-C24 alkaryl. and substituted C4-C23 alkheteroaryl;
wherein if Z is a substituted group, it is substituted by the one or more
substituents independently selected from the group consisting of -CN, -CO2R,
5'_C(O)NRIRI', =0, -OR'] -SR', -NO2. -NRR. -NRC(O) ']
-C(O)R] W
-NR5C(O)OR, CI-Clo alkyl, CI-Clo alkoxy, C3-CIO cycloalkyl, C-Clo heteroaryl,
C6-
C14 arYI, C4-C24 alkheteroaryl and C7-C24 alkaryl.
A is a heteroaryl moiety selected from the group consisting of
R R' Ra R I
N Rc N Rc NJN'%%'S S W:kS
I I I ==
R N IL) I N
R' R' R R
1
JNI.,0 N N N, N N
N 11
I =:= N
N
R R'
R R
0 S 0
1
N and S
Rb Rb
wherein
RI is selected from the group consisting of halogen, C3-Clo alkyl, C3-CIO
cycloalkyl, C1-CI3 heteroaryl, C6-14 aryl, C7-24 alkaryl, up to
per-halosubstituted Cj-
CIO alkyl, up to per-halosubstituted C3-CIO cycloalkyl, up to
per-halosubstituted CI-C13
heteroaryl, up to per-halosubstituted C6-14 aryl, and up to
per-halosubstituted C7-24
lo alkaryi;
3'
R2 is selected from the group consisting of H. -C(O)R], -CO2R], -C(O)NWR
CI-CIO alkYl. C3-CIO cycloaRcyl, C7-C24 alkaryl, C4-C23 alkheteroaryl,
substituted Cj-
CIO alkyl, substituted C3-CIO cycloalkyl, substituted C7-C24 alkaryl and
substituted C4-
C23 alkheteroaryl,
where W is a substituted group, it is substituted by one or more substituents
independently selected from the group consisting of -CN, - C02R], -C(O)-WR3',
'NO2, -OR], -SR], and-halogen up to per-halosubstitution,
wherein R 3 and R3' are independently selected from the group consisting of
H,
-OW, -SW9 -NWW'] -C(O)W, -CO2R4, -C(0)N1eW'q CI-CIO alkYl, C3-CIO CYClOalkyl,
C6-CI4 arYl, C3-CI3 heteroaryl, C7-C24 alkaryl, C4-C23 alkheteroaryl, up to
per-
halosubstituted CI-CIO alkyl, up to per-halosubstituted C3-CIO cycloalkyl, up
to per-
halosubstituted C6-CI4 aryl. and up to per-halosubstituted C3-C,3 heteroaryl;
and
wherein R] and R]'are independently selected from the group consisting of H,
CI-Clo alkyl, C3-CIO cycloalkyl, C6-CI4 aryl, C3-CI3 heteroaryl.; C7-C24

alkaryl, C4-C23
aMeteroaryl, up to per-halosubstituted CI-Clo alkyl, up to
per-halosubstituted C3-CIO
cycloalkyl, up to per-halosubstituted C6-CI4 aryl and up to
per-halosubstituted C3-CI3
heteroaryl,
V is CI-CIO alkYl, C3-CIO cycloalkyl, up to per-halosubstituted CI-CIO alkyl
io . and up to per-halosubstituted C3-CIO cycloalkyl; and
R] is hydrogen or halogen,
R' is hydrogen, halogen, CI-Clo alkyl, up to per-halosubstituted CI-CIO alkyl
or combines with R' and the ring carbon atoms to which R1 and W are bound to
form
a 5- or 6-membered cycloalkyl, aryl or hetaryl ring with 0-2 members selected
from
0.) N and S.

2 A method as in claim 1, wherein B is up to a tricyclic aromatic ring
structure selected from the group consisting of
Xn Xn
0 0
R5 R5
N N
and
which is substituted or unsubstituted by halogen, up to per-halosubstitution,
and
wherein n = 0-3 and each X - is independently selected from the group
consisting of -CN, -CO2R, -C(O)NWR. -C(O)R', -NO2. -OR'q - SR'] - i]R5R5'9
-NR'C(O)QR 5'q -NWC(O)W'] Ci-Clo alkyl, C2-lo-alkenyl, C1 alkoxy, C3-CIO
cycloalkyl, C6-CI4 arYl, C7-C24 alkaryl, C3-CI3 heteroaryl, C4-C23
aRdieteroaryl, and
substituted CI-Clo alkyl, substituted C2 alkenyl, substituted CI alkoxy,
substituted C3-CIO cycloalkyl, substituted C4-C23 alkheteroaryl and -Y-Ar;
wherein if X is a substituted group, it is substituted by one or more
substituents independently selected from the group consisting of -CN, -CO2R'q
-C(O)R', -C(O)NRR5', -OR, -SR, -NRR , NO2, -NRC(O)R. -NRC(O)OR and
io halogen up to per-halosubstitution;
wherein R5 and R5' are independently selected from H, C I -C 1 o alkyl, C2.1
0-
alkenyl, C3-CIO cycloalkryl, C6-CI4 aryl, C3-CI3 heteroaryl, C7-C24 alkaryl,
C4-C23
alkheteroaryl, up to per-halosubstituted CI-Clo alkyl, up to
per-halosubstituted C2
alkenyl, up to per-halosubstituted C3-CIO cycloalkyl, up to
per-halosubstituted C6-CJ4
aryl. and up to per-halosubstituted C3-CI3 heteroaryl,
wherein Y is - O-, -S-, -N(W)-] -(CH2)-mi -C(O)-9 -CH(OH)-q -(CH2)m&]
_NR5C(O)NR5R5'_, _NR5C(O)_, _C(O)NRI_, -(CH2)MS-1 -(CH2)mN(R)-] -O(CH2)m-]
_CHXa. _CXa 2-] -S-(CH2)m- and -N(R5)(CH2)m-i
m = 1-3, and Xa is halogen; and
Ar is a 5-10 member aromatic structure containing 0-4 members of the group
consisting of nitrogen, oxygen and sulfur which is unsubstituted or
substituted by
halogen up to per-halo and optionally substituted by Znj, wherein nI is 0 to
3 and each
Z is independently selected from the group consisting of -CN, -CO2R, -C(O)R,
--Oq
_SO2R'q _SO2NjeRI'. _C(O)NR5R5', 'C(O)R59 'NO2. -OR, -SR, -NRR,
-NRC(O)OR. -NRC(O)R5', CI-Clo alkyl, CI-Clo alkoxy, C3-CIO cycloalkyl, C6-CI4
aryl, C3-CI3 heteroaryl, C7-C24 alkaryl, C4-C23 alkheteroaryl, substituted
CI-Clo alkylq

substituted C3-CIO cycloalkyl, substituted C7-C24 alkaryl. and substituted
C4-C23
alkheteroaryl; wherein if Z is a substituted group, it is substituted by one
or more
substituents independently selected from the group consisting of -CN, -CO2W,
-C(O)NRR, =O, -OR, -SR, -NO2. -NRR5' . -NRC(O)R. -NRC(O)OR, CI-CI0
alkyl, CI-Clo alkoxy, C3-CIO cycloalkyl, C-Clo heteroaryl, C6-CI4 aryl,
C4-C24
alkheteroaryl and C7-C24 alkaryl.
, A method of claim 1, wherein B is
X
n
(V] Qts]Znl
wherein Y is selected from the group consisting of , -S-, -CH2-, -SCH2-,
-CH2S', -CH(OH)-, -C(O)-, -CXa2, -CXaH-, -CH20- and -OCH2-, where X' is
halogen,
Q is a six member aromatic structure containing 0-2 nitrogen, substituted or
unsubstituted by halogen, up to per-halosubstitution;
Q1 is a mono- or bicyclic aromatic structure of 3 to 10 carbon atoms and 0-4
members of the group consisting of N, 0 and S, unsubstituted or unsubstituted
by
halogen up to per-halosubstitution, and
X, Z, n and nI are as defined in claim 1 and s is 0 or 1.

4 A method as in claim 3, wherein
Q is phenyl. or pyridinyl, substituted or unsubstituted by halogen, up to
per-
halosubstitution,
Q1 is selected from the group consisting of phenyl, pyridinyl, naphthyl,
pyrimidinyl, quinoline, isoquinoline, imidazole and benzothiazolyl,
substituted or
unsubstituted by halogen, up to per-halo substitution, or -Y-Ql is
phthalimidinyl
substituted or unsubstituted by halogen up to per-halo substitution, and
Z and X are independently selected from the group consisting of -R6, -OR]
2o and -NHR7, wherein R6 is hydrogen, Cl-Clo-alkyl or C3-Clo-cycloalkyl and R
7 is
selected from the group consisting of hydrogen, C3-Clo-alkyl,
C3-C6-cycloalkyl and
C6-CIO-aryl, wherein R6 and R7 can be substituted by halogen or up to per-
halosubstitution.

5 A method as in claim 1, comprising administering a compound of the
formula
R'
N
I 0
N I I
R NH-C-NH-B
wherein R' and R2 and B are as defined in claim 1.

6 A method as in claim 5, wherein B is 2,3-dichlorophenyl or of the formula
X
n
U - (Y__ Q'ts-Zn 1
wherein Q is phenyl, Q1 is phenyl or pyridinyl, Y is , -S-, -CH2- or -SCH2, X
is
CF3, and Z is -OH, -Cl or NHC(O)-C,,H2p+1, where p = 2-4, s = 0 or 1, n = 0
and n1
0 or 1.

7 A method as in claim I comprising administering a compound selected from the group consisting of-
N-(3-tert-Butyl pyrazolyl)-N'-(4-(2,3-dichlorophenyl)urea;
N-(3-tert-Butyl pyrazolyl)-N]-(3-(4-pyridinyl)thiophenyl)urea;
N-(3-tert-Butyl pyrazolyl)-N]-(4-(4-pyridinyl)methylphenyl)urea;
N-(3-tert-Butyl pyrazolyl)-N-(4-(4-pyridinyl)oxyphenyl)urea;
N-(3-tert-Butyl pyrazolyl)-N'-(4-(4-pyridinyl)thiophenyl)urea;
N-(3-tert-Butyl pyrazolyl)-N'-(4-(4-pyridinyl)methylphenyl)urea;
N-(l-Methyl tert-butyl pyrazolyl)-N'-(2,3-dichlorophenyl)urea;
N-(l-Methyl tert-butyl pyrazolyl)-N'-(4-(4-hydroxy-phenyl)thiophenyl)urea;
N-(l-Methyl tert-butyl pyrazolyl)-N'-(4-(4-ethylaininocarbonyl-phenyl)oxyphenyl)urea;
N-(I-Methyl tert-butyl pyrazolyl)-N]-(4-(4-isobutylaminocarbonyl-phenyl)thiophenyl)urea;
N-(I-Methyl tert-butyl pyrazolyl)-N-(4-(4-pyridinyl)thiophenyl)urea;
N-(l-Methyl tert-butyl pyrazolyl)-N'-(3-(4-pyridinyl)thiophenyl)urea;
N-(l-Methyl tert-butyl pyrazolyl)-N]-(4-(4-pyridinyl)thio -(trifluoro-methyl)phenyl)urea;
N-(I-Methyl tert-butyl pyrazolyl)-N]-(4-(4-pyridinyl)oxyphenyl)urea;
N-(I-Methyl tert-butyl pyrazolyl)-N]-(4-((4-pyridinyl)methylthio)-phenyl)urea;
N-(I-(2,2,2-Trifluoroethyl) tert-butyl pyrazolyl)-N]-(2,3-dichloro-phenyl)urea;
N-(l-(2-Hydroxyethyl) tert-butyl pyrazolyl)-N'-(2,3-dichlorophenyl)urea;
N-(I-Etboxycarbonylmethyl tert-butyl pyrazolyl)-N]-(2,3-dichloro-phenyl)urea;
N-(I-(2-Cyanoethyl) tert-butyl pyrazolyl)-N'-(2,3-dichlorophenyl)urea;
N-(I-(3-Hydroxyphenyl)methyl tert-butyl pyrazolyl)-N'-(2,3-dichloro-phenyl)urea;
N-(l-Cyclohexyl tert-butyl pyrazolyl)-N]-(4-(4-pyridinyl)methyl-io phenyl) urea;
N-(l-methyl3-phenyl pyrazolyl)-N'-(3-(4-(2-methylcarbamoyl)-pyridyl)thiophenyl) urea;
N-(I-methyl tert-butyl pyrazolyl)-N'-(4-(4-pyridyl)thiophenyl) urea;
N-(l-methyl tert-butyl pyrazolyl)-N'-(3-(4-pyridyl)thiophenyl) urea;
N-(I-methyl tert-butyl pyrazolyl)-N]-(3-trifluoromethyl (4-pyridylthio)phenyl) urea;
N-(3-tert-butyl pyrazolyl)-N'-(3-(4-pyridyl)oxyphenyl) urea;
N-(3-tert-butyl pyrazolyl)-N'-(4-(4-pyridyl)oxyphenyl) urea;
and pharmaceutically acceptable salts thereof

8 A method as in claim 5, wherein R' is t-butyl.

9 A method as in claim I comprising administering a compound of the formula
R
0 0
N H - B
wherein R1 and B are as defined in claim 1.
. A method as in claim 9, wherein B is
X
n
(Y-- Qls-Zn 1
wherein Q is phenyl, Q1 is phenyl or pyridinyl, Y is --O-, -S- or -CH2, X is CF3, Z is
OH] CH3, - O-CpH2p+1, wherein n = 2-6 or -C(O)-NH-CH3, S = 1, n = 0 or 1 and nI
0 or 1.

11 A method as in claim 1 comprising administering a compound selected from the group consisting of-
N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-hydroxyphenyl)oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-isopropoxyphenyl)oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N-(4-(4-isobutoxyphenyl)oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-pentyloxyphenyl)oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-methylaininocarbonylphenyl)-oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N'-(3-(4-pyridinyl)thiophenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N-(3-(4-pyridinyl)oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)thiophenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)methylphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)thio (trifluoromethyl)-phenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N'-(3-(3-methyl pyridinyl)thiophenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N]-(3-(3-methyl pyridinyl)oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N'-(4-(3-methyl pyridinyl)oxyphenyl)urea;
N-(5-tert-Butyl isoxazolyl)-N'-(4-(3-methyl pyridinyl)thiophenyl)urea;
N-(5-tert-butyl isoxazolyl)-N-(4-(4-(2-methylcarbamoyl)pyridyl)-oxyphenyl) urea;
N-(5-tert-butyl isoxazolyl)-N'-(3-(4-(2-methylcarbamoyl)-pyridyl)oxyphenyl) urea;
N-(5-tert-butyl isoxazolyl)-N'-(4-(4-(2-carbamoyl)pyridyl)oxyphenyl) urea;
N-(5-tert-butyl isoxazolyl)-N-(3-(4-(2-carbamoyl)pyridyl)oxyphenyl) urea;
N-(5-tert-butyl isoxazolyl)-N]-(3-((4-pyridyl)fluoromethyl)phenyl) urea;
N-(5-tert-butyl isoxazolyl)-N]-(3-((4-pyridyl)oxomethyl)phenyl) urea;
and pharmaceutically acceptable salts thereof

12 A method as in claim 9, wherein R1 is t-Butyl.

13 A method as in claim I comprising administering a compound of the formula
R'
N 0
1 1 1

0 NH-C M-B
wherein R1 and B are as defined in claim 1.

14 A method as in claim 13, wherein B is 2,3-dichlorophenyl or of the formula
x
I n
Q - (Y__ Qt_Zn 1
wherein Q is phenyl, Q1 is phenyl, pyridinyl or benzothiazolyl, Y is , -S-, -CH2-
or -NH-, Z is Cl, -CH3 or -OCH3, s = 0 or 1, n = 0 and n1 = 0 or 1.

15 A method as in claim 13, wherein R1 is t-butyl.

16 A method as in claim 1 comprising administering a compound selected from the group consisting of :
N-(3-Isopropyl isoxazolyl)-N-(3-(4-pyridinyl)thiophenyl)urea;
N-(3-tert-Butyl isoxazolyl)-N]-(2,3-dichlorophenyl)urea;
N-(3-tert-Butyl isoxazolyl)-N'-(4-(4-methoxyphenyl)aminophenyl)urea;
N-(3-tert-Butyl isoxazolyl)-N'-(4-(4-methoxyphenyl)oxyphenyl)urea;
N-(3-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)oxyphenyl)urea;
N-(3-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)thiophenyl)urea;

N-(3-tert-Butyl isoxazolyl)-N-(4-(4-pyridinyl)methylphenyl)urea;
N-(3-(1,1-Diinethylpropyl) isoxazolyl)-N]-(4-(4-pyridinyl)methyl-
phenyl)urea;
N-(3-(1,1-Dimethylpropyl) isoxazolyl)-N]-(3-(4-pyridinyl)thiophenyl)urea;
N-(3-(1,1-Dimethylpropyl) isoxazolyl)-N]-(4-(2-benzothiazolyl)-
oxyphenyl)urea;
N-(3-(I-Methyl-l-ethylpropyl) isoxazolyl)-N]-(4-(4-pyridinyl)oxy-
phenyl)urea;
N-(3-(I-Methyl-l-ethylpropyl) isoxazolyl)-N]-(4-(4-pyridinyl)methyl-
phenyl)urea;
N-(3-cyclobutylyl isoxazolyl)-N'-(4-(4-pyridyl)oxyphenyl) urea;
N-(3-tert-butyl isoxazolyl)-N'-(4-(4-pyridyl)thiophenyl) urea;
N-(3-(l-methyl-l-ethylprop yl) isoxazolyl)-N-(4-(4-pyridyl)oxyphenyl)
urea;
N-(3-tert-butyl isoxazolyl)-N'-(4-(4-pyridyl)methylphenyl) urea;
N-(3-tert-butyl isoxazolyl)-N'-(4-(4-methoxyphenyl)aminophenyl) urea;
and pharmaceutically acceptable salts thereof

17 A method as in claim I comprising administering a compound of the
formula
R1
S 0
INH-C-NH-B
Rb
wherein R1, R] and B are as defined in claim 1.
. A method as in claim 17, wherein B is of the formula
X
n
Q']s-Zni
wherein Q is phenyl, Q1 is phenyl or pyridinyl, Y is or -S- or -CH2-, Z is
OH,
CH3, Cl, -OC2H5 or -OC3H7, s = 0 or 1, n = 0 and n1 = 0 or 1.

19 A method as in claim 17, wherein R1 is t-butyl.

20 A method as in claim 17, wherein R] is hydrogen.

21 A method as in claim 1 comprising administering a compound selected
from the group consisting of-
N-(2-Bromo tert-butyl thienyl)-N'-(4-methylphenyl)urea;
N-(5-tert-Butyl thienyl)-N'-(2,3-dichlorophenyl)urea;
N-(5-tert-Butyl thienyl)-N'-(4-(4-hydroxyphenyl)oxyphenyl)urea;
N-(5-tert-Butyl thienyl)-N]-(4-(4-ethoxyphenyl)oxyphenyl)urea;
N-(5-tert-Butyl thienyl)-N'-(4-(4-isopropoxyphenyl)oxyphenyl)urea;
N-(5-tert-Butyl thienyl)-N'-(4-(3-pyridinyl)oxyphenyl)urea;
N-(5-tert-Butyl thienyl)-N'-(4-(4-pyridinyl)oxyphenyl)urea;
N-(5-tert-Butyl thienyl)-N'-(4-(4-pyridinyl)thiophenyl)urea;
N-(5-tert-Butyl thienyl)-N-(4-(4-pyridinyl)methylphenyl)urea;
N-(5 -tert-butyl (l -tWa-3,4-diazolyl))-N-(4-(4-pyridyl)oxyphenyl) urea;
N-(5-tert-butyl (I-thia-3,4-diazolyl))-N'-(3-(4-pyridyl)thiophenyl) urea;
N-(5-tert-butyl (l-thia-3,4-diazolyl))-N'-(3-(4-methoxyphenyl)oxyphenyl)
urea;
N-(5-tert-butyl (1 -thia-3,4-diazolyl))-N]-(3-(4-methylphenyl)oxyphenyl)
urea;
N-(5-tert-butyl thienyl)-N]-(4-(4-pyridyl)oxyphenyl) urea;
N-(5-tert-butyl thienyl)-N'-(4-(4-pyridyl)thiophenyl) urea.;
N-(5-tert-butyl thienyl)-N!-(4-(4-pyridyl)methylphenyl) urea;
N-(5-tert-butyl tWenyl)-N'](2,3-dichlorophenyl) urea.;
N-(5-tert-butyl thienyl)-N'-(4-(4-hydroxyphenyl)oxyphenyl) urea;
N-(5-tert-butyl thienyl)-N]-(4-(4-methoxyphenyl)oxyphenyi) urea;

N-(5-tert-butyl thienyl)-N-(4-(4-ethoxyphenyl)oxyphenyl) urea;
N-(5-tert-butyl thienyl)-N]-(4-(4-isopropoxyphenyl)oxyphenyl) urea;
and pharmaceutically acceptable salts thereof

22 A method as in claim 1 comprising administering a compound of the formula
Ra
N 0
N I-qH-C-I-qH-B
wherein R' and B are as defined in claim 1.

23 A method as in claim 22, wherein B is of the formula
X-n
-U-(Y-Q'-)-s-Zni
'wherein Q is phenyl, Q1 is phenyl or pyridinyl, Y is --O-, -S- or CH2-, CI, -OC2H5 or
-OC3H7, s = 0 or 1, n = 0 and n1 is 0 or 1.

24 A method as in claim 22, wherein R' is CF3- or t-butyl.

25 A method as in claim 1 comprising administering a compound of one of the formulae
R1
0 0
11
RI RI
S 0 0
II or 11
rqH-C-NH-B NH-C-NH-B
wherein R', R] and B are as defined in claim 1.

26 A method as in claim 25, wherein B is of the formula
X
n
-U--(Y- Q)-s-Zni
wherein Q is phenyl, Q1 is phenyl or pyridinyl, Y is --O- , -S- or -CH2-, Z is OH, CH3,
Cl, -OC2H5 or -OC3H7, s = 0 or 1, n = 0 and n1 is 0 or 1.

27 A method as in claim 25, wherein R1 is t-butyl.

28 A method as in claim 1, wherein the compound for formula I displays p38 activity (IC5o) better than 1 0]im as determined by an in-vitro kinase assay.

29 A method according to claim 1, wherein the disease is mediated by a cytokine or protease regulated by p3 8.

30 A method according to claim 1, comprising administering an amount of a compound of formula I effective to inhibit p38.

31 A method according to claim 1, comprising administering an amount of a compound of formula I effective to inhibit production of a disease-mediating cytokine
or protease.

32 A method according to claim 1, wherein the disease is mediated by TNFa, MAT-1, MNT-3, IL-1, EL-6 or EL
. A method according to claim 1, wherein the disease is an inflammatory or immunomodulatory disease.

34 A method according to claim 1, wherein the disease is rheumatoid arthritis, osteoporosis, osteoarthritis, asthma, septic shock, inflammatory bowel
disease, or the result of host-versus-graft reactions.

35 A compound of one of the formulae
a)
t-BU
N 0
1 H_11 H
0 N C-N 0 0- CH2--O
b)
t-Bu
0
1] 0
N 11
INH-C-Nw-] 0--] R6
wherein R6 is CH2-phenyl, -NH-C(O)-O-t-butyl, n-pentyl , n-butyl , -C(O)-N(CH3)2, CH2CH(CH3)2 or n-propyl;
C)
R'
N 0
N]C-N 0 CH3
H
wherein R1 is -CH2-t-butyl;
2o d)
t-Bu
N 0
1 11
N n-U-Imn
R
C1 C1
wherein R] is -CH2CF3, -C2H4 -OH, -CH2-(3-HOC6H4)j CH2C(O)NHCH3, -CH2C(O)OC2H5, -C2114CN, or
] CH2
0
1 1
O-CANH
cl cl
e)
t-Bu
N 0 0
1 H 11 H II
N C-N-] -C-O-C4H9
CH3
f)
t-Bu
0
NH-C-NHC] 0]-OCH(CH02
g)
Br
N 0
11 11 ·
S- NH-C-NH-] CH3
or
h)
CH(CH3)2
CH3
N

I 0
U 11
NH-C-NH
C1 C1
and pharmaceutically acceptable salts thereof
. A pharmaceutical composition comprising a compound according to claim 35 or a pharmaceutically acceptable salt thereof and a physiologically acceptable carrier.

37 A method as in claim 1, comprising administering a compound of the formula
R'
N,:]ko
0
IN =-] I I
NH-C-NH-B
wherein R I and B are as defined in claim 1.

38 A method as in claim I comprising administering a compound of the formula
R1
0
NH-C-NH-B
wherein R' and B are as defined in claim 1.

39 A method as in claim 1, comprising administering a compound of the formula
R1
W]]k S
0
L-=-J, II
Imn-U-Nn-B
wherein R1, R2 and B are as defined in claim 1.

40 A method as in claim 1, comprising administering a compound of the formula
R1
I
N N*,N
k 0
N.... 11
NH-C-NH-B
wherein R' and B are as defined in claim 1.

41 A method as in claim 1, comprising administering a compound of the formula
R'
0
S I I
NH-C-NH-B
wherein R1 and B are as defined in claim 1.

=>

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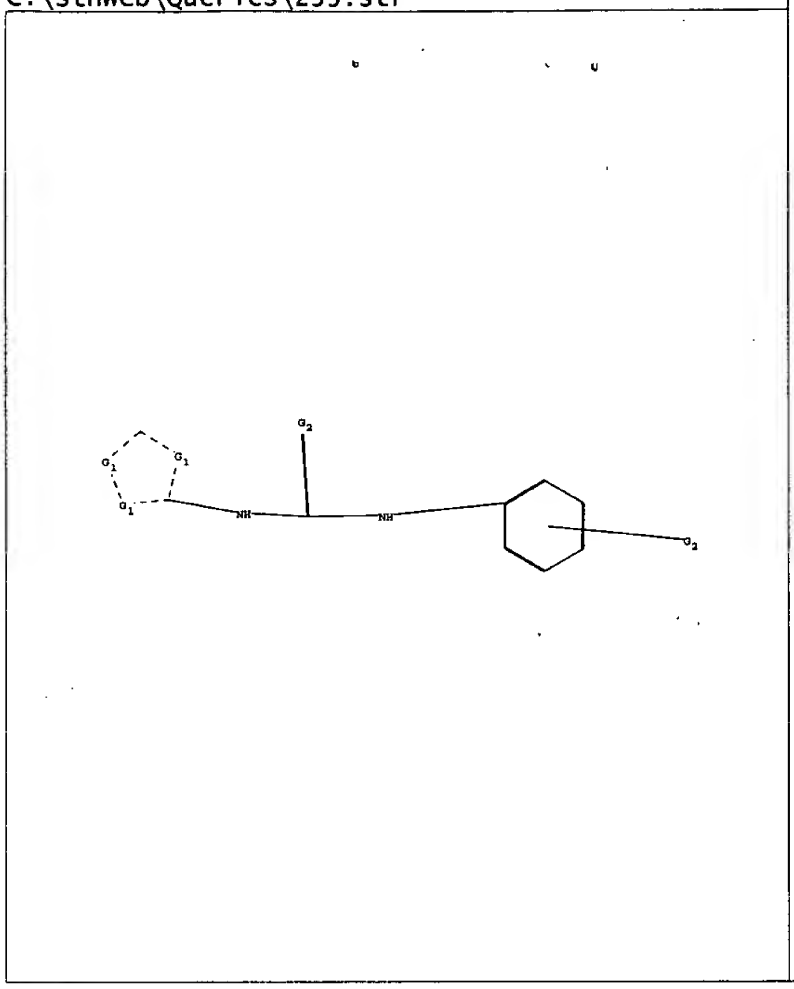

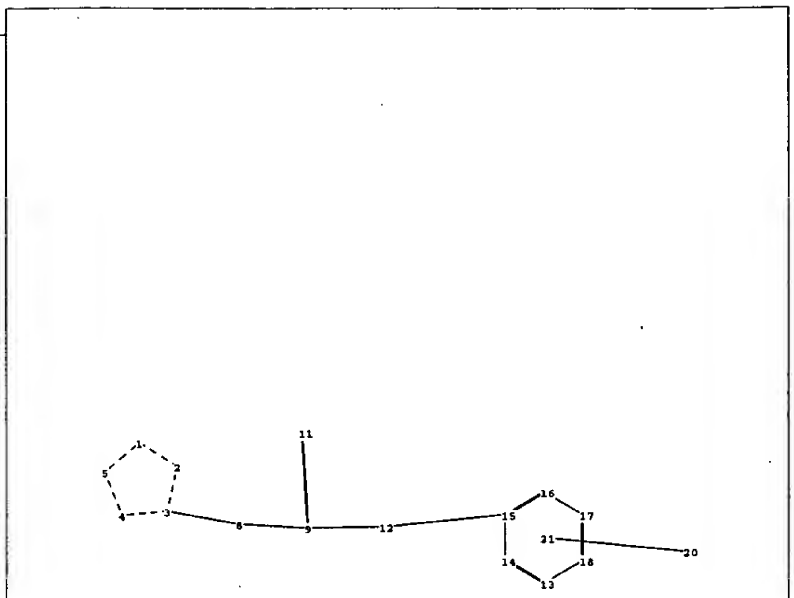

chain nodes :
8 9 11 12 20
ring nodes :
1 2 3 4 5 13 14 15 16 17 18
chain bonds :
3-8 8-9 9-11 9-12 12-15
ring bonds :
1-2 1-5 2-3 3-4 4-5 13-14 13-18 14-15 15-16 16-17 17-18
exact/norm bonds :
1-2 1-5 2-3 3-4 3-8 4-5 8-9 9-11 9-12 12-15
normalized bonds :
13-14 13-18 14-15 15-16 16-17 17-18
isolated ring systems :
containing 1 : 13 :

G1:C,O,N

G2:O,S

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 8:CLASS 9:CLASS 11:CLASS 12:CLASS 13:Atom
14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 20:CLASS 21:CLASS

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 NEWS  1            Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2            "Ask CAS" for self-help around the clock
 NEWS  3   SEP 09   CA/CAplus records now contain indexing from 1907 to the
                    present
 NEWS  4   DEC 08   INPADOC: Legal Status data reloaded
 NEWS  5   SEP 29   DISSABS now available on STN
 NEWS  6   OCT 10   PCTFULL: Two new display fields added
 NEWS  7   OCT 21   BIOSIS file reloaded and enhanced
 NEWS  8   OCT 28   BIOSIS file segment of TOXCENTER reloaded and enhanced
 NEWS  9   NOV 24   MSDS-CCOHS file reloaded
 NEWS 10   DEC 08   CABA reloaded with left truncation
 NEWS 11   DEC 08   IMS file names changed
 NEWS 12   DEC 09   Experimental property data collected by CAS now available
                    in REGISTRY
 NEWS 13   DEC 09   STN Entry Date available for display in REGISTRY and CA/CAplus
 NEWS 14   DEC 17   DGENE: Two new display fields added
 NEWS 15   DEC 18   BIOTECHNO no longer updated
 NEWS 16   DEC 19   CROPU no longer updated; subscriber discount no longer
                    available
 NEWS 17   DEC 22   Additional INPI reactions and pre-1907 documents added to CAS
                    databases
 NEWS 18   DEC 22   IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
 NEWS 19   DEC 22   ABI-INFORM now available on STN
 NEWS 20   JAN 27   Source of Registration (SR) information in REGISTRY updated
                    and searchable
 NEWS 21   JAN 27   A new search aid, the Company Name Thesaurus, available in
                    CA/CAplus
 NEWS 22   FEB 05   German (DE) application and patent publication number format
                    changes
 NEWS 23   MAR 03   MEDLINE and LMEDLINE reloaded
 NEWS 24   MAR 03   MEDLINE file segment of TOXCENTER reloaded
 NEWS 25   MAR 03   FRANCEPAT now available on STN
 NEWS 26   MAR 29   Pharmaceutical Substances (PS) now available on STN
 NEWS 27   MAR 29   WPIFV now available on STN
 NEWS 28   MAR 29   No connect hour charges in WPIFV until May 1, 2004
 NEWS 29   MAR 29   New monthly current-awareness alert (SDI) frequency in RAPRA

 NEWS EXPRESS  MARCH 5 CURRENT WINDOWS VERSION IS V7.00A, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 3 MARCH 2004
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
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FILE 'HOME' ENTERED AT 21:09:03 ON 29 MAR 2004
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COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 21:09:18 ON 29 MAR 2004
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   28 MAR 2004  HIGHEST RN 668418-93-7
DICTIONARY FILE UPDATES:  28 MAR 2004  HIGHEST RN 668418-93-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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L1 HAS NO ANSWERS
L1                STR
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 C 17 O 18 N 19
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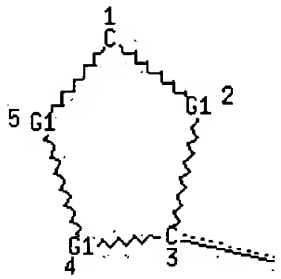
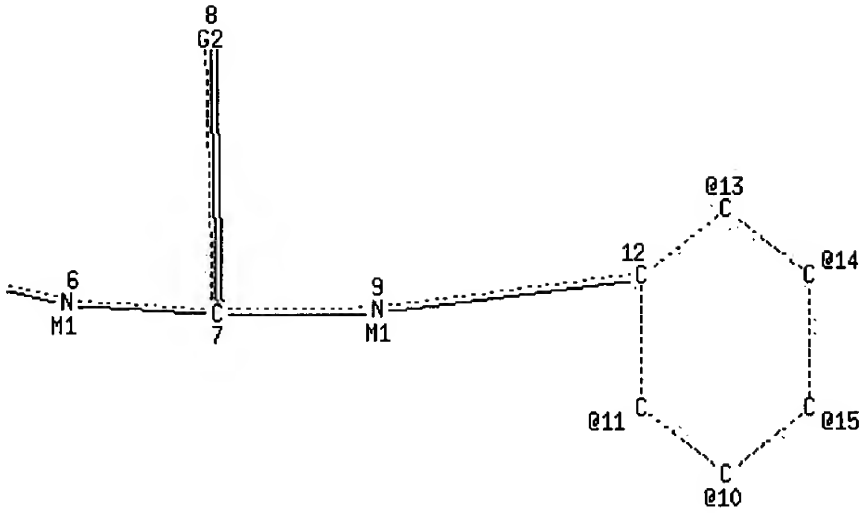


Page 1-A



Page 1-B

G2 @16

Page 1-C

VAR G1=17/18/19

VAR G2=20/21

VPA 16-10/11/13/14/15 S

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NSPEC	IS R	AT	3
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NSPEC	IS C	AT	16

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MLEVEL IS CLASS AT 6 7 9 20 21

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RSPEC I

NUMBER OF NODES IS 21

STEREO ATTRIBUTES: NONE

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SAMPLE SCREEN SEARCH COMPLETED - 8160 TO ITERATE

12.3% PROCESSED 1000 ITERATIONS 2 ANSWERS

INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)

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SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       157787 TO   168613
PROJECTED ANSWERS:             84 TO      568

L2            2 SEA SSS SAM L1

=> s l1 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 21:10:32 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 163349 TO ITERATE

100.0% PROCESSED  163349 ITERATIONS                          787 ANSWERS
SEARCH TIME: 00.00.03

L3          787 SEA SSS FUL L1

=> file hcaplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                             155.84     156.05

FILE 'HCAPLUS' ENTERED AT 21:10:37 ON 29 MAR 2004
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FILE COVERS 1907 - 29 Mar 2004  VOL 140 ISS 14
FILE LAST UPDATED: 28 Mar 2004  (20040328/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> d his

     (FILE 'HOME' ENTERED AT 21:09:03 ON 29 MAR 2004)

     FILE 'REGISTRY' ENTERED AT 21:09:18 ON 29 MAR 2004
L1              STRUCTURE UPLOADED
L2            2 S L1
L3          787 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 21:10:37 ON 29 MAR 2004

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L4          46 L3/THU
                (L3 (L) THU/RL)

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          665 DUMAS, J?/AU
L5          5 L4 AND DUMAS, J?/AU

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L5   ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2004 ACS on STN
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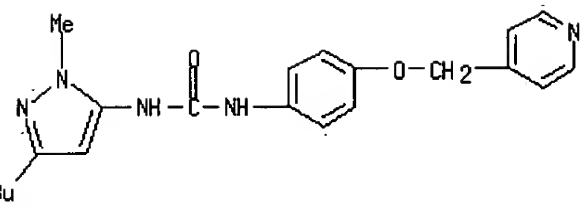
Full Text | Citing References

ACCESSION NUMBER: 2002:407968 HCAPLUS
DOCUMENT NUMBER: 138:49372
TITLE: Synthesis and pharmacological characterization of a potent, orally active p38 kinase inhibitor
AUTHOR(S): **Dumas, Jacques**; Hatoum-Mokdad, Holia; Sibley, Robert N.; Smith, Roger A.; Scott, William J.; Khire, Uday; Lee, Wendy; Wood, Jill; Wolanin, Donald; Cooley, Jeffrey; Bankston, Donald; Redman, Aniko M.; Schoenleber, Robert; Caringal, Yolanda; Gunn, David; Romero, Romulo; Osterhout, Martin; Paulsen, Holger; Housley, Timothy J.; Wilhelm, Scott M.; Pirro, John; Chien, Du-Shieng; Ranges, Gerald E.; Shrikhande, Alka; Muzsi, Andrew; Bortolon, Elizabeth; Wakefield, Jean; Gianpaolo Ostravage, Cynthia; Bhargava, Ajay; Chau, Thuy
CORPORATE SOURCE: Department of Chemistry Research, Bayer Research Center, West Haven, CT, 06516, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2002), 12(12), 1559-1562
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Inhibitors of the MAP kinase p38 provide a novel approach for the treatment of osteoporosis, inflammatory disorders, and cancer. We have identified N-(3-tert-butyl-1-methyl-5-pyrazolyl)-N'-(4-(4-pyridinylmethyl)phenyl)urea as a potent and selective p38 kinase inhibitor in biochem. and cellular assays. This compd. is orally active in two acute models of cytokine release (TNF-induced IL-6 and LPS-induced TNF) and a chronic model of arthritis (20-day murine collagen-induced arthritis).

IT 229001-93-8
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(structure-activity relationship, synthesis and pharmacol. characterization of a potent, orally active p38 kinase inhibitors)
RN 229001-93-8 HCAPLUS
CN Urea, N-[3-(1,1-dimethylethyl)-1-methyl-1H-pyrazol-5-yl]-N'-[4-(4-pyridinylmethoxy)phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:425745 HCAPLUS
DOCUMENT NUMBER: 131:87909
TITLE: Inhibition of p38 kinase activity using substituted heterocyclic ureas
INVENTOR(S): **Dumas, Jacques**; Khire, Uday; Lowinger, Timothy Bruno; Paulsen, Holger; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Lee, Wendy; Redman, Aniko
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932111	A1	19990701	WO 1998-US26080	19981222
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2315720	AA	19990701	CA 1998-2315720	19981222
AU 9919971	A1	19990712	AU 1999-19971	19981222
AU 739642	B2	20011018		
EP 1041982	A1	20001011	EP 1998-964709	19981222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001526223	T2	20011218	JP 2000-525102	19981222

PRIORITY APPLN. INFO.: US 1997-995750 A 19971222
WO 1998-US26080 W 19981222

OTHER SOURCE(S): MARPAT 131:87909
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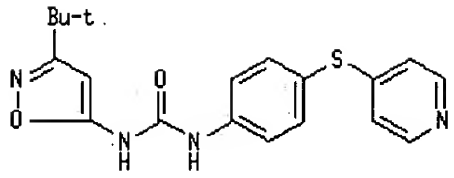


II

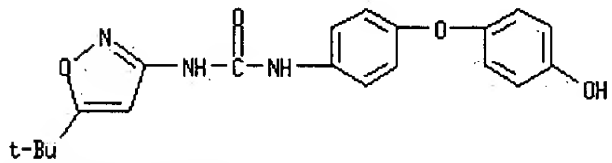
AB A method for treatment of p38-mediated disease other than cancer comprises administration of ANHCONHB [I; A = substituted isoxazolyl, pyrazolyl, thienyl, furyl; B = (substituted) mono-, di-, or tricyclic aryl, heteroaryl contg. ≥1 5-6 membered arom. structure contg. 0-4 N, O, or S atoms]. Reaction of 4-(4-pyridinylthio)aniline with 3-tert-butyl-5-isoxazolyl isocyanate in toluene gave title compd. II. In an in vitro p38 kinase assay, I displayed IC50 values of 1-10 μM.

IT **228999-08-4P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); **THU (Therapeutic use)**; **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of substituted heterocyclic ureas for treatment of p38 kinase-mediated diseases other than cancer)

RN 228999-08-4 HCAPLUS

CN Urea, N-[5-(1,1-dimethylethyl)-3-isoxazolyl]-N'-[4-(4-hydroxyphenoxy)phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:425744 HCAPLUS
DOCUMENT NUMBER: 131:73649
TITLE: Preparation of pyrazolyl aryl ureas and related compounds as p38 kinase inhibitors
INVENTOR(S): **Dumas, Jacques**; Khire, Uday; Lowinger, Timothy Bruno; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Redman, Aniko; Sibley, Robert
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932110	A1	19990701	WO 1998-US26079	19981222

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,

KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,
MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2315647	AA	19990701	CA 1998-2315647	19981222
AU 9919970	A1	19990712	AU 1999-19970	19981222
AU 762077	B2	20030619		
EP 1043995	A1	20001018	EP 1998-964708	19981222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001526222	T2	20011218	JP 2000-525101	19981222

PRIORITY APPLN. INFO.: US 1997-995751 A 19971222
WO 1998-US26079 W 19981222

OTHER SOURCE(S): MARPAT 131:73649
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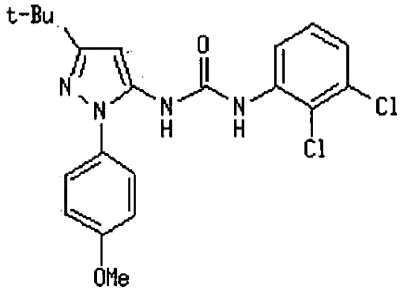
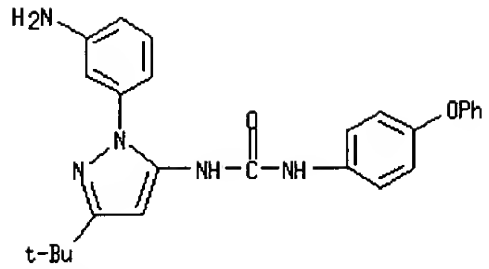


II

AB A method for treatment of p38-mediated disease other than cancer comprises administration of ANHCONHB [I; A = substituted pyrazolyl, thienyl, furyl; B = (substituted) mono-, di-, or tricyclic aryl, heteroaryl contg. ≥1 5-6 membered arom. structure contg. 0-4 N, O, or S atoms]. Reaction of 2,3-dichlorophenyl isocyanate with 1-(4-methoxyphenyl)-3-tert-butyl-5-aminopyrazole in toluene gave title compd. II. In an in vitro p38 kinase assay, I displayed IC50 values of 1-10 μM.

IT 227623-07-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); **THU (Therapeutic use)**; **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of pyrazolyl aryl ureas and related compds. as p38 kinase inhibitors)

RN 227623-07-6 HCAPLUS
CN Urea, N-[1-(3-aminophenyl)-3-(1,1-dimethylethyl)-1H-pyrazol-5-yl]-N'-(4-phenoxyphenyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:425740 HCAPLUS
DOCUMENT NUMBER: 131:73648
TITLE: Inhibition of raf kinase using substituted heterocyclic ureas
INVENTOR(S): **Dumas, Jacques**; Khire, Uday; Lowinger, Timothy Bruno; Paulsen, Holger; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Lee, Wendy; Redman, Aniko
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 163 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932106	A1	19990701	WO 1998-US26078	19981222
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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2315717	AA	19990701	CA 1998-2315717	19981222
AU 9921989	A1	19990712	AU 1999-21989	19981222
EP 1047418	A1	20001102	EP 1998-965981	19981222
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JP 2001526220	T2	20011218	JP 2000-525097	19981222
BR 9814374	A	20020514	BR 1998-14374	19981222
NO 2000003232	A	20000821	NO 2000-3232	20000621
BG 104597	A	20010228	BG 2000-104597	20000712

PRIORITY APPLN. INFO.: US 1997-996343 A 19971222
WO 1998-US26078 W 19981222

OTHER SOURCE(S): MARPAT 131:73648
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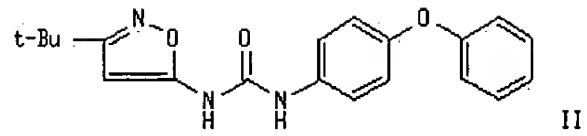


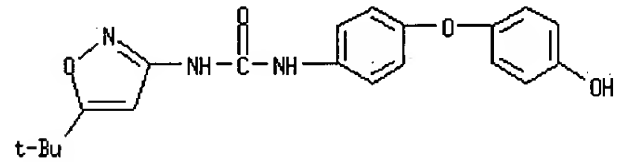
II

AB A method for treatment of cancerous cell growth mediated by raf kinase comprises administration of urea derivs. ANHCONHB [I; A = substituted isoxazolyl, thienyl, thiadiazolyl, furyl, pyrazolyl, etc.; B = (substituted) mono-, di-, or tricyclic aryl, heteroaryl contg. ≥1 5-6 membered arom. structure contg. 0-4 N, O, or S atoms]. Reaction of 4-phenyloxyphenyl isocyanate with 5-amino-3-tert-butylisoxazole in methylene chloride and heating at reflux temp. for 2 days gave title compd. II. In an in vitro raf kinase assay, I displayed IC50 values of 1-10 μM.

IT 228999-08-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); **THU (Therapeutic use)**; **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of substituted heterocyclic ureas for treatment of cancerous cell growth mediated by raf kinase)

RN 228999-08-4 HCAPLUS

CN Urea, N-[5-(1,1-dimethylethyl)-3-isoxazolyl]-N'-[4-(4-hydroxyphenoxy)phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:421660 HCAPLUS
DOCUMENT NUMBER: 131:44811
TITLE: Preparation of aryl- and heteroaryl-substituted heterocyclic ureas as raf kinase inhibitors
INVENTOR(S): **Dumas, Jacques**; Khire, Uday; Lowinger, Timothy Bruno; Paulsen, Holger; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Redman, Aniko; Sibley, Robert
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932455	A1	19990701	WO 1998-US26082	19981222

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,

DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,
MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2315713	AA	19990701	CA 1998-2315713	19981222
AU 9919055	A1	19990712	AU 1999-19055	19981222
AU 765412	B2	20030918		
EP 1056725	A1	20001206	EP 1998-963810	19981222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9814361	A	20011127	BR 1998-14361	19981222
JP 2001526269	T2	20011218	JP 2000-525392	19981222
CN 1117081	B	20030806	CN 1998-812504	19981222
NZ 505845	A	20031031	NZ 1998-505845	19981222
NO 2000003231	A	20000822	NO 2000-3231	20000621
BG 104598	A	20010228	BG 2000-104598	20000712

PRIORITY APPLN. INFO.: US 1997-996181 A 19971222
WO 1998-US26082 W 19981222

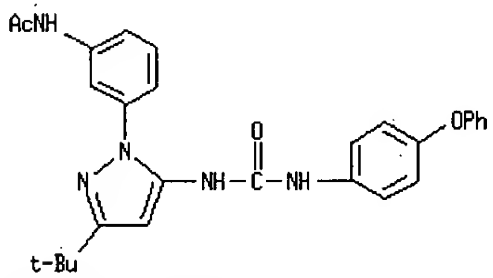
OTHER SOURCE(S): MARPAT 131:44811

AB The title compds. ANHCONHB (A = heteroaryl; B = aryl, heteroaryl), raf kinase inhibitors, were prepd. E.g., N-(1-phenyl-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinylmethyl)phenyl)urea was prepd.

IT **227623-06-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aryl- and heteroaryl-substituted heterocyclic ureas as raf kinase inhibitors)

RN 227623-06-5 HCAPLUS

CN Acetamide, N-[3-[3-(1,1-dimethylethyl)-5-[[[(4-phenoxyphenyl)amino]carbonyl]amino]-1H-pyrazol-1-yl]phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FILE 'REGISTRY' ENTERED AT 21:09:18 ON 29 MAR 2004
L1 STRUCTURE UPLOADED
L2 2 S L1
L3 787 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 21:10:37 ON 29 MAR 2004

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L4            46 S L3/THU
L5             5 S L4 AND DUMAS, J?/AU

=> s l4 not l5
L6            41 L4 NOT L5

=> s l6 and khire, u?/au
              40 KHIRE, U?/AU
L7             0 L6 AND KHIRE, U?/AU

=> s l6 and lowinger, t?/au
              41 LOWINGER, T?/AU
L8             1 L6 AND LOWINGER, T?/AU

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L8   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
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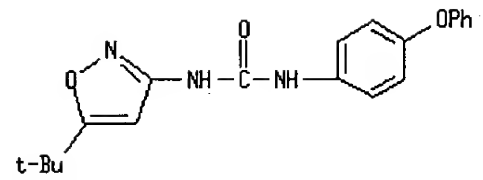
Full Text | Citing References

ACCESSION NUMBER: 2001:746592 HCAPLUS
DOCUMENT NUMBER: 136:95577
TITLE: Discovery of heterocyclic ureas as a new class of raf kinase inhibitors: identification of a second generation lead by a combinatorial chemistry approach
AUTHOR(S): Smith, R. A.; Barbosa, J.; Blum, C. L.; Bobko, M. A.; Caringal, Y. V.; Dally, R.; Johnson, J. S.; Katz, M. E.; Kennure, N.; Kingery-Wood, J.; Lee, W.; **Lowinger, T. B.**; Lyons, J.; Marsh, V.; Rogers, D. H.; Swartz, S.; Walling, T.; Wild, H.
CORPORATE SOURCE: Department of Chemistry Research, Bayer Research Center, West Haven, CT, 06516, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2001), 11(20), 2775-2778
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Heterocyclic ureas, such as N-3-thienyl N'-aryl ureas, have been identified as novel inhibitors of raf kinase, a key mediator in the ras signal transduction pathway. Structure-activity relationships were established, and the potency of the screening hit was improved 10-fold to IC50=1.7 μM. A combinatorial synthesis approach enabled the identification of a breakthrough lead (IC50=0.54 μM) for a second generation series of heterocyclic urea raf kinase inhibitors.

IT 228998-90-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(heterocyclic ureas as raf kinase inhibitors)
RN 228998-90-1 HCAPLUS
CN Urea, N-[5-(1,1-dimethylethyl)-3-isoxazolyl]-N'-(4-phenoxyphenyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FILE 'REGISTRY' ENTERED AT 21:09:18 ON 29 MAR 2004
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L2 2 S L1
L3 787 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 21:10:37 ON 29 MAR 2004
L4 46 S L3/THU
L5 5 S L4 AND DUMAS, J?/AU
L6 41 S L4 NOT L5
L7 0 S L6 AND KHIRE, U?/AU
L8 1 S L6 AND LOWINGER, T?/AU

=> s l6 and paulsen, h?/au
660 PAULSEN, H?/AU
L9 1 L6 AND PAULSEN, H?/AU

=> s l6 not l8
L10 40 L6 NOT L8

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660 PAULSEN, H?/AU
L11 1 L10 AND PAULSEN, H?/AU

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L11 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1998:776671 HCAPLUS
DOCUMENT NUMBER: 130:38286
TITLE: Inhibition of p38 kinase activity by aryl ureas
INVENTOR(S): Ranges, Gerald; Scott, William; Bombara, Michael; Rauner, Deborah; Redman, Aniko; Smith, Roger; **Paulsen, Holger**; Chen, Jinshan; Gunn, David; Renick, Joel
PATENT ASSIGNEE(S): Bayer Corp., USA; et al.
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9852558	A1	19981126	WO 1998-US10375	19980521

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9875854	A1	19981211	AU 1998-75854	19980521	
EP 1019040	A1	20000719	EP 1998-923600	19980521	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2001526687	T2	20011218	JP 1998-550617	19980521	
US 6344476	B1	20020205	US 1998-83396	19980522	
US 2002103253	A1	20020801	US 2001-947761	20010907	

PRIORITY APPLN. INFO.:

US 1997-863022	A2	19970523
US 1997-98557P	P	19970523
WO 1998-US10375	W	19980521
US 1998-83396	A3	19980522

OTHER SOURCE(S): MARPAT 130:38286
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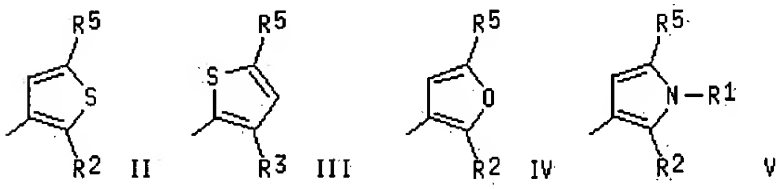
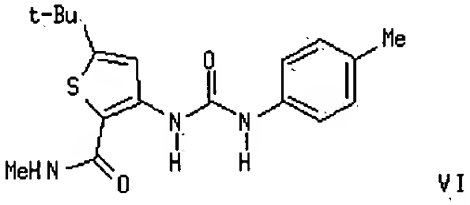


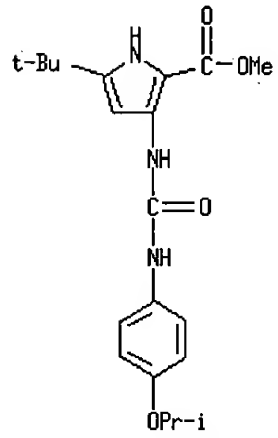


AB The title ureas ANHC(O)NHB [I; A = (un)substituted C6-12 aryl, C5-12 heteroaryl; B = II-V; R1 = H, C1-4 alkyl; R2, R3 = halo, COOR1, CN, etc.; R5 = C3-5 alkyl], useful in treating cytokine mediated diseases other than cancer and proteolytic enzyme mediated diseases other than cancer, were prepd. Thus, reaction of N-methyl-3-amino-5-tert-butylthiophene-2-carboxamide (prepn. given) with 4-methylphenyl isocyanate in PhMe afforded 44% the title compd. VI. Compds. I are useful in treating diseases mediated by TNFα, MMP-1, MMP-3, IL-1, IL-6, or IL-8 such as rheumatoid arthritis, osteoporosis, asthma, septic shock, inflammatory bowel disease, or the result of host-vs.-graft reactions. All exemplified compds. I showed p38 IC50s of 1 nM - 10 μM.

IT 216573-97-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibition of p38 kinase activity by aryl ureas)

RN 216573-97-6 HCAPLUS

CN 1H-Pyrrole-2-carboxylic acid, 5-(1,1-dimethylethyl)-3-[[[[4-(1-methylethoxy)phenyl]amino]carbonyl]amino]-, methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FILE 'REGISTRY' ENTERED AT 21:09:18 ON 29 MAR 2004
L1 STRUCTURE UPLOADED
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L3 787 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 21:10:37 ON 29 MAR 2004
L4 46 S L3/THU
L5 5 S L4 AND DUMAS, J?/AU
L6 41 S L4 NOT L5
L7 0 S L6 AND KHIRE, U?/AU
L8 1 S L6 AND LOWINGER, T?/AU
L9 1 S L6 AND PAULSEN, H?/AU
L10 40 S L6 NOT L8
L11 1 S L10 AND PAULSEN, H?/AU

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L12 39 L10 NOT L11

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163 RIEDL, B?/AU
L13 0 L12 AND RIEDL, B?/AU

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1938 SCOTT, W?/AU
L14 0 L12 AND SCOTT, W?/AU

=> **s l12 and smith, r?/au**
13382 SMITH, R?/AU
L15 0 L12 AND SMITH, R?/AU

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           7563 JOHNSON, J?/AU
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             14 RENICK, J?/AU
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L1                STRUCTURE UPLOADED
L2              2 S L1
L3            787 S L1 FULL

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L4             46 S L3/THU
L5              5 S L4 AND DUMAS, J?/AU
L6             41 S L4 NOT L5
L7              0 S L6 AND KHIRE, U?/AU
L8              1 S L6 AND LOWINGER, T?/AU
L9              1 S L6 AND PAULSEN, H?/AU
L10            40 S L6 NOT L8
L11             1 S L10 AND PAULSEN, H?/AU
L12            39 S L10 NOT L11
L13             0 S L12 AND RIEDL, B?/AU
L14             0 S L12 AND SCOTT, W?/AU
L15             0 S L12 AND SMITH, R?/AU
L16             0 S L12 AND WOOD, W?/AU
L17             0 S L12 AND HATOUM-MOKDAD, H?/AU
L18             0 S L12 AND JOHNSON, J?/AU
L19             0 S L12 AND LEE, W?/AU
L20             0 S L12 AND REDMAN, A?/AU
L21             0 S L12 AND SIBLEY, R?/AU
L22             0 S L12 AND RENICK, J?/AU

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         240211 CANC?
L23             5 L12 AND  CANC?
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L23  ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2004 ACS on STN
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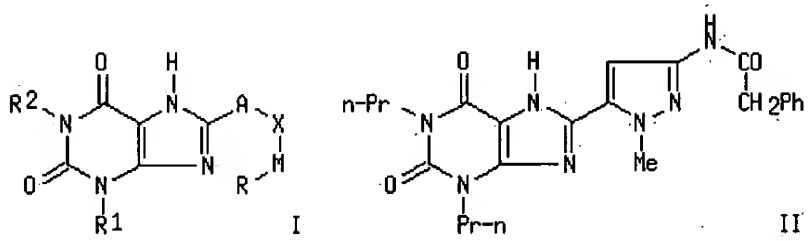
Full Text | Citing References

ACCESSION NUMBER: 2003:610209 HCAPLUS
DOCUMENT NUMBER: 139:164659
TITLE: Preparation of 8-heteroarylxanthine adenosine A2B receptor antagonists for use in pharmaceutical compositions
INVENTOR(S): Baraldi, Pier Giovanni; Borea, Pier A.
PATENT ASSIGNEE(S): King Pharmaceuticals Research and Development, Inc., USA
SOURCE: PCT Int. Appl., 135 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003063800	A2	20030807	WO 2003-US3224	20030203
WO 2003063800	A3	20031224		
US 2003207879	A1	20031106	US 2003-357865	20030203

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-353317P P 20020201
OTHER SOURCE(S): MARPAT 139:164659
GI



AB 8-Heteroarylxanthines, such as I [R = aryl, heteroaryl, amino, carboxy, NO2, OH, etc; R1, R2 = H, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl; R3 = H, alkyl, alkenyl, alkynyl; A = bond, alkylene, alkenylene, alkynylene; M = bond, carbonyl contg. alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, heteroalkynylene, etc.; X = 5 or 6 membered heterocyclic ring], were prepd. for therapeutic use as adenosine A2B receptor antagonists. These 8-heteroarylxanthines are useful for treatment of autoimmune, inflammatory, and vascular diseases which are mediated by adenosine A2B receptors such as, retinal vascular diseases, acute inflammatory diseases involving degranulation of mast

cells including asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, allergic rhinitis, allergic dermatitis and bee sting, impaired sensitivity to insulin including type 2 diabetes or non-insulin dependent diabetes, pre-diabetic state, impaired glucose tolerance, diseases in which angiogenesis is a key component of pathogenesis, including solid tumors and angiogenic retinopathy, apnea of pre-term infants, myocardial reperfusion injury, inflammatory bowel disease, multiple sclerosis, and lupus erythematosis. Thus, II was prepd. via a cyclocondensation reaction of 1-methyl-3-(benzyloxycarbonylamino)pyrazole-5-carboxylic acid with 1,3-dipropyl-5,6-diaminouracil using EDCI in MeOH to form the pyrazolylxanthine moiety and subsequent N-acylation with phenylacetic acid using thionyl chloride and Et3N in CH2Cl2. The prepd. xanthines were tested for affinity to human A1, A2A, A2B, and A3 adenosine receptors.

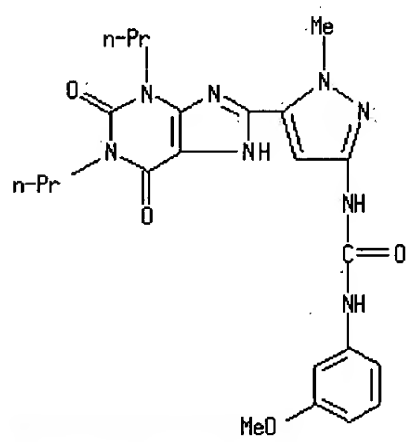
IT 574754-45-3P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of 8-heteroarylxanthine adenosine A2B receptor antagonists for use in pharmaceutical compns. for treatment of inflammatory, autoimmune and retinal vascular diseases)

RN 574754-45-3 HCAPLUS

CN Urea, N-(3-methoxyphenyl)-N'-[1-methyl-5-(2,3,6,7-tetrahydro-2,6-dioxo-1,3-dipropyl-1H-purin-8-yl)-1H-pyrazol-3-yl]- (9CI) (CA INDEX NAME)



L23 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:849617 HCAPLUS
DOCUMENT NUMBER: 137:370101
TITLE: Preparation of quinoline derivatives having azolyl group and quinazoline derivatives as antitumor agents
INVENTOR(S): Kubo, Kazuo; Sakai, Teruyuki; Nagao, Rika; Fujiwara, Yasunari; Isoe, Toshiyuki; Hasegawa, Kazumasa
PATENT ASSIGNEE(S): Kirin Beer Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2002088110 A1 20021107 WO 2002-JP4279 20020426
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
JP 2003012668 A2 20030115 JP 2002-126869 20020426
US 2003087907 A1 20030508 US 2002-132473 20020426
EP 1382604 A1 20040121 EP 2002-724651 20020426
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
NO 2003004595 A 20031219 NO 2003-4595 20031014
PRIORITY APPLN. INFO.: JP 2001-132775 A 20010427
WO 2002-JP4279 W 20020426
OTHER SOURCE(S): MARPAT 137:370101
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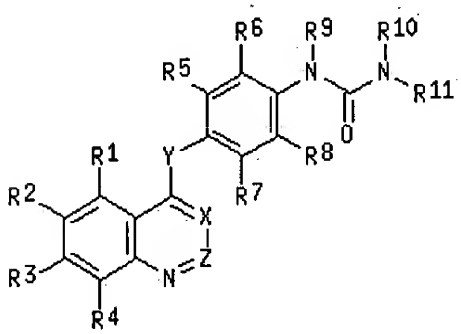


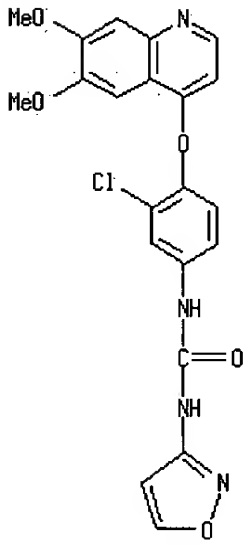
I

AB N-[(4-quinolinyl or 4-quinazolinyl)thio or -oxy]phenyl-N'-azolylurea derivs. represented by the formula (I) or pharmaceutically acceptable salts or solvates thereof [wherein X, Z = CH, N; Y = O, S; R1, R2, R3 = H, NO2, NH2, each (un)substituted C1-6 alkyl or alkoxy or C2-6 alkenyl or alkynyl; R4 = H; R5-R8 = H, halo, C1-4 alkyl, alkoxy, or alkylthio, CF3, NO2, NH2; R9, R10 = C1-6 alkyl, each (un)substituted C1-4 alkylcarbonyl or C1-6 alkyl; R11 = (un)substituted azolyl] are prepd. These compds. are useful for the treatment of tumor, diabetic retinopathy, chronic articular rheumatism, psoriasis, atherosclerosis , and Kaposi's sarcoma. They are also used for inhibiting neovascularization of a target blood vessel by contacting them with vascular endothelial cells of the target blood vessel. Thus, 100 mg 2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]aniline was dissolved in 5 mL CHCl3 and 0.5 mL Et3N, treated with a soln. of 100 mg triphosgene in CHCl3, and stirred at room temp. for 15 min, followed by adding 49 mg 2-aminothiazole, and the resulting mixt. was stirred at room temp. overnight to give 31 mg N-[2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl]-N;-(1,3-thiazol-2-yl)urea (II). II at 20 mg/kg/day for 9 days inhibited the growth of human lung **cancer** transplanted in nude mice by 92.0%. The compds. I in vitro showed IC50 of 0.001-0.0697 μM for inhibiting the phosphorylation of the intracellular domain of human vascular endothelial cell growth factor (VEGF) receptor KDR (kinase insert domain-contg. receptor) in IH3T3 cell expressing human KDR.

IT **475108-15-7P**, N-[3-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-N'-(3-isoxazolyl)urea

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-[(4-quinolinyl or 4-quinazolinyl)oxy]phenyl-N'-azolylurea derivs. as neovascularization inhibitors for treatment of tumor, diabetic retinopathy, chronic articular rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma)

RN 475108-15-7 HCAPLUS
CN Urea, N-[3-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-3-isoxazolyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:314913 HCAPLUS
DOCUMENT NUMBER: 136:340689
TITLE: Preparation of urea derivatives containing nitrogenous aromatic ring compounds as inhibitors of angiogenesis
INVENTOR(S): Funahashi, Yasuhiro; Tsuruoka, Akihiko; Matsukura, Masayuki; Haneda, Toru; Fukuda, Yoshio; Kamata, Junichi; Takahashi, Keiko; Matsushima, Tomohiro; Miyazaki, Kazuki; Nomoto, Kenichi; Watanabe, Tatsuo; Obaishi, Hiroshi; Yamaguchi, Atsumi; Suzuki, Sachi; Nakamura, Katsuji; Mimura, Fusayo; Yamamoto, Yuji; Matsui, Junji; Matsui, Kenji; Yoshiba, Takako; Suzuki, Yasuyuki; Arimoto, Itaru
PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan
SOURCE: PCT Int. Appl., 699 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002032872	A1	20020425	WO 2001-JP9221	20011019

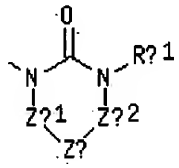
WO 2002032872 C1 20020926
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001095986	A5	20020429	AU 2001-95986	20011019
NO 2003001731	A	20030619	NO 2003-1731	20030414
US 2004053908	A1	20040318	US 2003-420466	20030418

PRIORITY APPLN. INFO.:

JP 2000-320420	A	20001020
JP 2000-386195	A	20001220
JP 2001-46685	A	20010222
WO 2001-JP9221	W	20011019

OTHER SOURCE(S): MARPAT 136:340689
GI

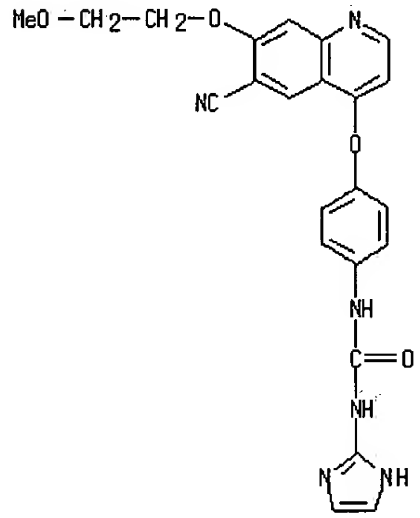
Q= 

AB N-aryl or N-heteroarylurea derivs. represented by the general formula Ag-Xg-Yg-Tg1 or salts thereof, or hydrates of both [wherein Ag = (un)substituted C6-14 aryl or 5- to 14-membered heterocyclic group; Xg = single bond, O, S, C1-6 alkylene, SO, SO2, (un)substituted NH; Yg = (un)substituted C6-14 aryl, 5- to 14-membered heterocyclic group, C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl-C1-6 alkyl, 5- to 14-membered heteroaryl-C1-6 alkyl, (CH2)gSO2 (g = 1-8), (CH2)faCH:CH(CH2)fb (fa, fb = 0, 1,2,3), etc.; and Tg1 = a group of the general formula -Eg-CO-NRg1(Zg) or Q; wherein Eg = a single bond, (un)substituted NH; Rg1 = H, (un)substituted C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-8 aliph. hydrocarbyl, etc.; Zg = C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl, etc.; Zg1, Zg2 = (a) a single bond, (b) C1-6 alkylene optionally having ≥1 atoms selected from O, S, and N in the middle or the terminus of the chain and optionally substituted with oxo, (c) (un)substituted C2-6 alkenyl] are prepd. These compds. are also inhibitors of vascular endothelial growth factor receptor kinase (VEGFR2 kinase) and are useful as antitumor agents against hemangioma, pancreatic **cancer**, stomach **cancer**, colon **cancer**, breast **cancer**, prostate **cancer**, lung **cancer**, brain tumor, leukemia, or ovarian **cancer**, as **cancer** metastasis inhibitors, and for the treatment of retina neovascularization, diabetic retinopathy, atherosclerosis, or inflammatory diseases such as osteoarthritis, rheumatoid arthritis, psoriasis, or delayed hypersensitivity. Thus, to soln. of 334 mg 4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenylamine in 4 mL DMF were added 0.066 mL pyridine and 0.102 mL Ph chlorocarbonate and stirred at room temp. for 2.5 h to give 330 mg N-[4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea which (260 mg) was hydrogenolyzed over platinum oxide in ethanol overnight to give 160 mg N-[4-[6-(4-hydroxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea (I). I showed IC50 of 0.02 nM

for inhibiting the vascular endothelial growth factor (VEGF)-stimulated sandwich tube formation in vascular endothelial cell.

IT 417713-01-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of urea derivs. contg. nitrogenous arom. ring compds. as angiogenesis inhibitors for prevention or treatment of diseases)

RN 417713-01-0 HCAPLUS
CN Urea, N-[4-[[6-cyano-7-(2-methoxyethoxy)-4-quinolinyl]oxy]phenyl]-N'-1H-imidazol-2-yl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:137022 HCAPLUS
DOCUMENT NUMBER: 134:193431
TITLE: 3(5)-Ureidopyrazole derivatives, processes for their preparation and their therapeutic uses including antitumor agents
INVENTOR(S): Pevarello, Paolo; Orsini, Paolo; Traquandi, Gabriella; Varasi, Mario; Fritzen, Edward L.; Warpehoski, Martha A.; Pierce, Betsy S.
PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy; Pharmacia & Upjohn Company
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012188	A1	20010222	WO 2000-US17878	20000811

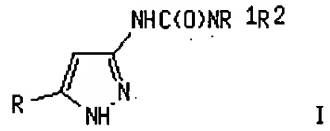
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,

LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6387900	B1	20020514	US 1999-372833	19990812
EP 1202734	A1	20020508	EP 2000-955241	20000811
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
BR 2000013277	A	20020618	BR 2000-13277	20000811
JP 2003507328	T2	20030225	JP 2001-516534	20000811
ZA 2002001118	A	20030310	ZA 2002-1118	20020208
NO 2002000687	A	20020403	NO 2002-687	20020211

PRIORITY APPLN. INFO.: US 1999-372833 A 19990812
WO 2000-US17878 W 20000811

OTHER SOURCE(S): MARPAT 134:193431
GI



I

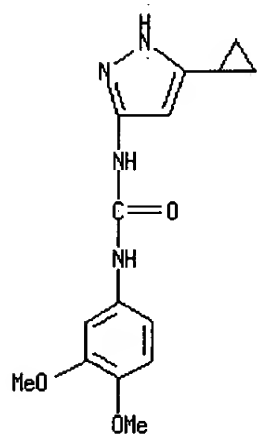
AB Compds. which are 3(5)-ureidopyrazole derivs. (I; e.g. N-(5-cyclopropyl-1H-pyrazol-3-yl)-N'-[2-(1-piperidinyl)ethyl]urea) or a pharmaceutically acceptable salt thereof, processes for their prepn. and their use as antitumor agents are claimed. In I: R = C1-C6 alkyl, aryl or arylalkyl group, which is optionally substituted with ≥1 OH, halogen, nitro, cyano, oxo, carboxy, amino, alkylamino, dialkylamino, alkylcarbonylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, aminocarbonylalkylamino, N-alkyl-N-carbonylamino, N-cycloalkyl-N-alkylaminoalkyl, aminoalkyl, aminocarbonyl, alkyl, cycloalkyl, alkylthio, alkoxy, alkylcarbonyl, alkylsulfonyl, alkylsulfonylamino, aminosulfonyl, alkoxycarbonyl, aryl, arylalkyl, aryloxy, arylthio, arylsulfonyl, arylamino, arylcarbonyl, N-alkylpiperazinyl, 4-morpholinyl, perfluorinated C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C2-C4 aminoalkynyl or C2-C4 hydroxyalkynyl substituents. R1 = -(CH2)n-R3. N = 0-4. R3 = H, OH, amino, cycloalkyl, aryl and heterocyclyl, which is optionally substituted with ≥1 OH, halogen, nitro, cyano, oxo, carboxy, amino, alkylamino, dialkylamino, alkylcarbonylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, aminocarbonylalkylamino, N-alkyl-N-carbonylamino, N-cycloalkyl-N-alkylaminoalkyl, aminoalkyl, aminocarbonyl, alkyl, cycloalkyl, alkylthio, alkoxy, alkylcarbonyl, alkylsulfonyl, alkylsulfonylamino, aminosulfonyl, alkoxycarbonyl, aryl, arylalkyl, aryloxy, arylthio, arylsulfonyl, arylamino, arylcarbonyl, N-alkylpiperazinyl, 4-morpholinyl, perfluorinated C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C2-C4 aminoalkynyl or C2-C4 hydroxyalkynyl substituents. R2 = H, or R2 and R1, together with the N atom to which they are bonded, form a heterocyclyl or heteroaryl group, which is optionally substituted with ≥1 OH, halogen, nitro, cyano, oxo, carboxy, amino, alkylamino, dialkylamino, alkylcarbonylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, aminocarbonylalkylamino, N-alkyl-N-carbonylamino, N-cycloalkyl-N-alkylaminoalkyl, aminoalkyl, aminocarbonyl, alkyl, cycloalkyl, alkylthio, alkoxy, alkylcarbonyl, alkylsulfonyl, alkylsulfonylamino, aminosulfonyl, alkoxycarbonyl, aryl, arylalkyl, aryloxy, arylthio, arylsulfonyl, arylamino, arylcarbonyl, N-alkylpiperazinyl, 4-morpholinyl, perfluorinated C1-C4 alkyl, C2-C4

alkenyl, C2-C4 alkynyl, C2-C4 aminoalkynyl or C2-C4 hydroxyalkynyl substituents. When n is 0 and R2 is H, R is a C3-C6 cycloalkyl group optionally substituted with a straight or branched C1-C6 alkyl group. The compds. are useful for the treatment of **cancer**, cell proliferative disorders, Alzheimer's disease, viral infections, auto-immune diseases or neurodegenerative diseases, but no quant. test results are presented. The **cancer** is selected from carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular **cancer** and Kaposi's sarcoma. The cell proliferative disorder is selected from benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation assocd. with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis. The method of treatment provides tumor angiogenesis and metastasis inhibition, cell cycle inhibition or cdk/cyclin dependent inhibition, and treatment or prevention of radiotherapy-induced or chemotherapy-induced alopecia. A process for prepg. I comprises : (a) reacting a 3-amino-5-R-1H-pyrazole with a R1NCO to produce a 1-R1NHC(O)-3-R1NHC(O)NH-5-R-1H-pyrazole and (b) selectively hydrolyzing this intermediate in a basic medium to produce I. Another method comprises (c) reacting a 1-tert-butoxycarbonyl-3-amino-5-R-1H-pyrazole with 4-nitrophenyl chloroformate, or a polymer supported form of 4-nitrophenyl chloroformate, to produce a 1-tert-butoxycarbonyl-3-(4-nitrophenoxycarbonylamino)-5-R-1H-pyrazole, or a polymer supported form; (d) reacting this intermediate with a R1R2NH to produce a 1-tert-butoxycarbonyl-3-(R1R2NC(O)NH)-5-R-1H-pyrazole; (e) hydrolyzing this compd. in acidic medium to produce I; and, optionally, converting the 3-ureidopyrazole deriv. into another deriv., and/or into a salt thereof.

IT 326920-53-0P, N-(5-Cyclopropyl-1H-pyrazol-3-yl)-N'-(3,4-dimethoxyphenyl)urea
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(ureidopyrazole derivs., processes for prepn. and therapeutic uses including antitumor agents)

RN 326920-53-0 HCAPLUS

CN Urea, N-(5-cyclopropyl-1H-pyrazol-3-yl)-N'-(3,4-dimethoxyphenyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

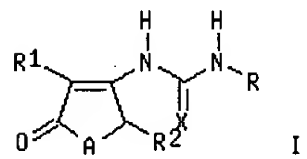
Full Text | Citing References

ACCESSION NUMBER: 1999:194134 HCAPLUS
DOCUMENT NUMBER: 130:237458
TITLE: Preparation of ureido and thioureido derivatives of 4-amino-2(5H)-furanones and 4-amino-2(5H)-thiophenones as antitumor agents
INVENTOR(S): Menta, Ernesto; Pescalli, Nicoletta; Conti, Marco; Zimmermann, Gerd
PATENT ASSIGNEE(S): Roche Diagnostics G.m.b.H., Germany
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9912917	A1	19990318	WO 1998-EP5524	19980901
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2302284	AA	19990318	CA 1998-2302284	19980901
AU 9895350	A1	19990329	AU 1998-95350	19980901
AU 748490	B2	20020606		
EP 1009747	A1	20000621	EP 1998-948889	19980901
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
BR 9812629	A	20000822	BR 1998-12629	19980901
JP 2001515894	T2	20010925	JP 2000-510725	19980901
ZA 9808096	A	20000322	ZA 1998-8096	19980904
US 6333346	B1	20011225	US 2000-485709	20000602
US 2002058694	A1	20020516	US 2001-986310	20011108

PRIORITY APPLN. INFO.:
EP 1997-115391 A 19970905
WO 1998-EP5524 W 19980901
US 2000-485709 A3 20000602

OTHER SOURCE(S): MARPAT 130:237458
GI



I

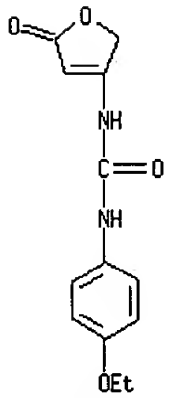
AB The title compds. [I; A = O, S; X = O, S; R1, R2 = H, alkyl; R = alkyl, cycloalkyl, alkylthio, etc.], useful as antitumor agents, esp. against colon **cancers**, were prepd. Thus, reaction of 4-chlorophenylurea with Et 4-chloroacetoacetate afforded I [A = O; X = O; R1 = R2 = H; R = 4-ClC6H4] which showed IC50 of 0.032 Tg/mL and of 0.034 Tg/mL against human colon **cancer** cell lines HT 29 and HCT 116, resp.

IT **221290-98-8P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of ureido and thioureido derivs. of 4-amino-2(5H)-furanones and 4-amino-2(5H)-thiophenones as antitumor agents)

RN 221290-98-8 HCAPLUS

CN Urea, N-(2,5-dihydro-5-oxo-3-furanyl)-N'-(4-ethoxyphenyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 21:09:03 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 21:09:18 ON 29 MAR 2004

L1 STRUCTURE UPLOADED
L2 2 S L1
L3 787 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 21:10:37 ON 29 MAR 2004

L4 46 S L3/THU
L5 5 S L4 AND DUMAS, J?/AU
L6 41 S L4 NOT L5
L7 0 S L6 AND KHIRE, U?/AU
L8 1 S L6 AND LOWINGER, T?/AU
L9 1 S L6 AND PAULSEN, H?/AU
L10 40 S L6 NOT L8
L11 1 S L10 AND PAULSEN, H?/AU
L12 39 S L10 NOT L11
L13 0 S L12 AND RIEDL, B?/AU
L14 0 S L12 AND SCOTT, W?/AU
L15 0 S L12 AND SMITH, R?/AU
L16 0 S L12 AND WOOD, W?/AU
L17 0 S L12 AND HATOUM-MOKDAD, H?/AU
L18 0 S L12 AND JOHNSON, J?/AU
L19 0 S L12 AND LEE, W?/AU
L20 0 S L12 AND REDMAN, A?/AU
L21 0 S L12 AND SIBLEY, R?/AU
L22 0 S L12 AND RENICK, J?/AU
L23 5 S L12 AND CANC?

=> s l12 not l23

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L24          34 L12 NOT L23

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             14 IBIB
         212191 ABS
              5 ABSES
         212196 ABS
                   (ABS OR ABSES)
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         261226 34
L25           0 L24, IBIB ABS FHITSTR, 1-34
                   ('L24'(W)IBIB(W)ABS(W)FHITSTR(W)1(W)34)

=> d l24, ibib abs fhitstr, 1-34

L24  ANSWER 1 OF 34  HCAPLUS  COPYRIGHT 2004 ACS on STN
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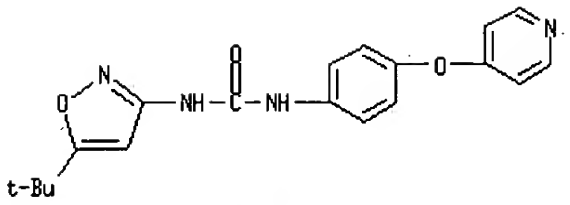
Full Text | Citing References

ACCESSION NUMBER: 2004:182368 HCAPLUS
TITLE: Three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands
INVENTOR(S): Come, Jon H.; Becker, Frank; Kley, Nikolai A.; Reichel, Christoph
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 238 pp., Cont.-in-part of U.S. Ser. No. 91,177.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004043388	A1	20040304	US 2002-234985		20020903
US 2003165873	A1	20030904	US 2002-91177		20020304
PRIORITY APPLN. INFO.:			US 2001-272932P	P	20010302
			US 2001-278233P	P	20010323
			US 2001-329437P	P	20011015
			US 2002-91177	A2	20020304

AB The invention provides compns. and methods for isolating ligand-binding polypeptides for a user-specified ligand, and for isolating small mol. ligands for a user-specified target polypeptide using an improved class of hybrid ligand compds. Prepn. of compds., e.g a methotrexate moiety linked by a polyethylene gycol moiety to dexamethasone, is described.

IT INDEXING IN PROGRESS
IT 228999-48-2D, conjugates
RL: BUU (Biological use, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands)
RN 228999-48-2 HCAPLUS
CN Urea, N-[5-(1,1-dimethylethyl)-3-isoxazolyl]-N'-[4-(4-pyridinyloxy)phenyl]- (9CI) (CA INDEX NAME)



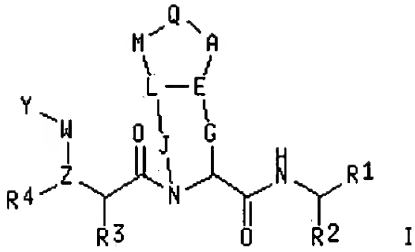
L24 ANSWER 2 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

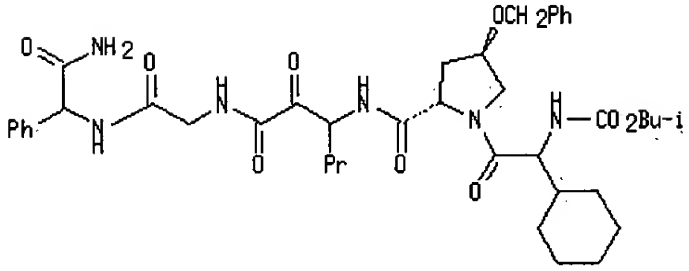
ACCESSION NUMBER: 2003:912843 HCAPLUS
DOCUMENT NUMBER: 139:381756
TITLE: Preparation of peptides as NS3-serine protease inhibitors of hepatitis C virus
INVENTOR(S): Saksena, Anil K.; Girijavallabhan, Viyyoor Moopil; Lovey, Raymond G.; Jao, Edwin; Bennett, Frank; Mccormick, Jinping L.; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Chan, Tin-Yau; Liu, Yi-tsung; Zhu, Zhaoning; Njoroge, F. George; Arasappan, Ashok; Parekh, Tejal; Ganguly, Ashit K.; Chen, Kevin X.; Venkatraman, Srikanth; Vaccaro, Henry A.; Pinto, Patrick A.; Santhanam, Bama; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita; Tamura, Susan Y.; Wu, Wanli; Hendrata, Siska; Huang, Yuhua
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 629 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003216325	A1	20031120	US 2001-908955	20010719
PRIORITY APPLN. INFO.:			US 2001-908955	20010719

OTHER SOURCE(S): MARPAT 139:381756
GI



I



II

AB The invention discloses novel peptides I [Y is alkyl, alkylaryl, heteroalkyl, heteroaryl, aryl- or alkylheteroaryl, cycloalkyl, alkyloxy, alkylaryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkylarylamino, arylamino, heteroarylamino, cycloalkylamino, or heterocycloalkylamino; R1 is acyl; Z is O, N, CH or CR; R, R2-R4 are H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halo, (cycloalkyl)alkyl, or (heterocycloalkyl)alkyl; W, Q, G, J, L, M independently may be present or absent; W is CO, CS, C(:N-CN), or SO2; Q is CH, N, P, alkylidene, O, NR, S, or SO2; A is O, CH, alkylidene, NR, S, SO2, or a bond; E is CH, N, alkylidene, or a double bond; G is alkylidene; J is alkylidene, SO2, NH, NR, or O; L is CH, CR, O, S, or NR; M is O, NR, S, SO2, or alkylidene (with provisos)] which have HCV protease inhibitory activity as well as methods for prepg. such compds. In another embodiment, the invention discloses pharmaceutical compns. comprising such compds. as well as methods of using them to treat disorders assocd. with the HCV protease. Thus, peptide II was prepd. by the solid-phase method and showed Ki = 1-100 nM (category A) in the HCV continuous assay.

IT **394723-07-0P**

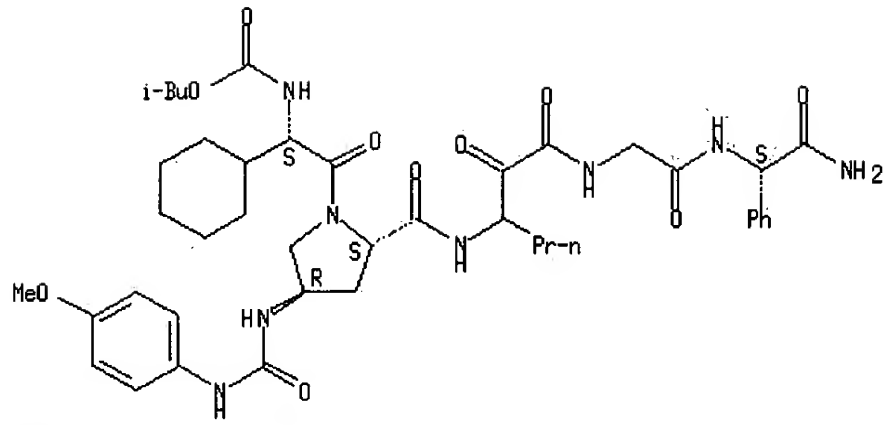
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of peptides as NS3-serine protease inhibitors of hepatitis C virus)

RN 394723-07-0 HCAPLUS

CN Glycinamide, (2S)-2-cyclohexyl-N-[(2-methylpropoxy)carbonyl]glycyl-(4R)-4-[[[(4-methoxyphenyl)amino]carbonyl]amino]-L-prolyl-3-amino-2-oxohexanoylglycyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L24 ANSWER 3 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:892762 HCAPLUS
DOCUMENT NUMBER: 139:395938
TITLE: Preparation of ureas as positive allosteric modulators of the nicotinic acetylcholine receptor
INVENTOR(S): Piotrowski, David W.; Rogers, Bruce N.; McWhorter, William W., Jr.; Walker, Daniel P.; Corbett, Jeffrey W.; Groppi, Vincent E., Jr.; Rudmann, Daniel G.
PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA
SOURCE: PCT Int. Appl., 159 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003093250	A2	20031113	WO 2003-US11493	20030428
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003236287	A1	20031225	US 2003-423062	20030425

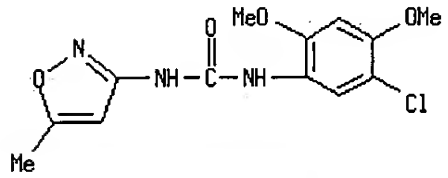
PRIORITY APPLN. INFO.: US 2002-377364P P 20020503
US 2003-456941P P 20030324

OTHER SOURCE(S): MARPAT 139:395938

AB ANHCXNHB [X = O, S; A = (un)substituted Ph, 6-membered N heteroaryl; B = (un)substituted 5-6-membered heteroaryl] were prepd. to treat diseases or conditions in which the α7 nAChR is known to be involved (no data). Thus, 2,4-Me(MeO)C6H3NH2 was treated with 3-F3CC6H4CNO to give 2,4-Me(MeO)C6H3NHCONHC6H4CF3-3.

IT 501925-31-1P
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of ureas as pos. allosteric modulators of the nicotinic

acetylcholine receptor)
RN 501925-31-1 HCAPLUS
CN Urea, N-(5-chloro-2,4-dimethoxyphenyl)-N'-(5-methyl-3-isoxazolyl)- (9CI) (CA INDEX NAME)



L24 ANSWER 4 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

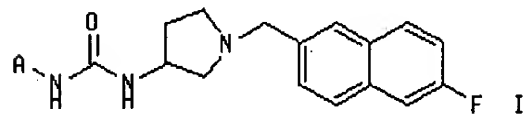
Full Text | Citing References

ACCESSION NUMBER: 2003:696868 HCAPLUS
DOCUMENT NUMBER: 139:230619
TITLE: Preparation of N-[1-(6-fluoronaphthalen-2-ylmethyl)pyrrolidin-3-yl]urea derivatives as CCR3 inhibitors
INVENTOR(S): Imaoka, Takayuki; Kawamura, Kuniaki; Kaneko, Masayuki; Kozono, Hideki; Morihira, Koichiro; Kubota, Hirokazu; Morokata, Tatsuaki; Kaneeda, Masanobu
PATENT ASSIGNEE(S): Toray Industries, Inc., Japan; Yamanouchi Pharmaceutical Co., Ltd.
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003072545	A1	20030904	WO 2003-JP2227	20030227

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2002-51900 A 20020227
JP 2003-20822 A 20030129
OTHER SOURCE(S): MARPAT 139:230619
GI



AB Cyclic amine compds. represented by the general formula (I) [wherein A is

a group which is selected from the group consisting of substituted aryls, substituted heterocyclic groups, and substituted cycloalkyls, has at least one substituent X, and may have at least one substituent Y (wherein the substituent X is selected from the group consisting of HO-(C1-6 alkyl), HO-(C2-6 alkyl)-O-(C1-6 alkyl), HO2C-(C1-6 alkyl), (C1-6 alkyl)-OCO-(C1-6 alkyl), H2NCO-(C1-6 alkyl), (C1-3 alkyl)2NCO-(C1-6 alkyl), (C1-3 alkyl)-CONH-(C1-6 alkyl), HO2C-(C1-6 alkyl)-O-(C1-6 alkyl), etc., and the substituent Y is selected from the group consisting of halogeno, C1-3 alkyl, OH, methoxy, CN, and CF3)] or pharmaceutically acceptable salts thereof are prepd. These compds. are C-C chemokine receptor 3 (CCR-3) inhibitors and useful for the treatment of inflammatory diseases, inflammatory cell infiltration, and diseases caused by eosinophil infiltration. They are excellent in oral absorbability. Thus, 3-[3-(tert-butyldimethylsilyloxy)propoxy]phenylamine was dissolved in MeCN, treated with NaHCO3, cooled with ice, treated with 4-nitrophenyl chloroformate, stirred at room temp. for 1 h, cooled in ice, treated with (R)-1-[(6-fluoronaphthalen-2-yl)methyl]pyrrolidin-3-ylamine and Et3N, stirred at room temp. overnight to give N-[3-[3-(tert-butyldimethylsilyloxy)propoxy]phenyl]-N'-[(R)-1-[(6-fluoronaphthalen-2-yl)methyl]pyrrolidin-3-yl]urea which was treated with Bu4NF in THF at room temp. for 2 h to give 89% N-[3-(3-hydroxypropoxy)phenyl]-N'-[(R)-1-[(6-fluoronaphthalen-2-yl)methyl]pyrrolidin-3-yl]urea (II). II inhibited the human eotaxin-induced increase in cellular Ca+ ion concn. in human CCR3-transformed B300-19 cell with IC50 of 38 nM.

IT **592551-76-3P**

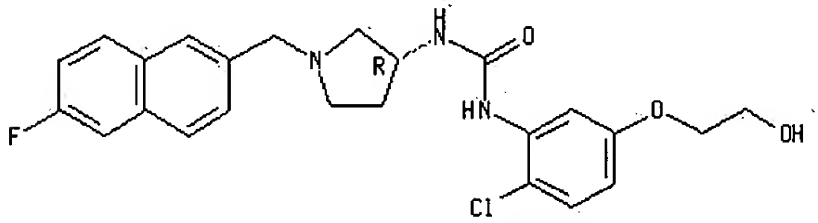
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of N-[(fluoronaphthalenylmethyl)pyrrolidinyl]urea derivs. as CCR3 inhibitors for treatment of inflammations, inflammatory cell infiltration, and diseases caused by eosinophil infiltration)

RN 592551-76-3 HCAPLUS

CN Urea, N-[2-chloro-5-(2-hydroxyethoxy)phenyl]-N'-[(3R)-1-[(6-fluoro-2-naphthalenyl)methyl]-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 5 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:591204 HCAPLUS

DOCUMENT NUMBER: 139:149928

TITLE: Preparation of peptides as NS3-serine protease inhibitors of hepatitis C virus

INVENTOR(S): Saksena, Anil K.; Girijavallabhn, Viyyoor M.; Lovey, Raymond G.; Jao, Edwin; Bennett, Frank; McCormick, Jinping L.; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Chan, Tin-yau; Liu, Yi-tsung; Zhu, Zhaoning; Njoroge, George F.; Arasappan, Ashok;

Parekh, Tejal; Ganguly, Ashit K.; Chen, Kevin X.; Venkatraman, Srikanth; Vaccaro, Henry A.; Pinto, Patrick A.; Santhanam, Bama; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita; Tamura, Susan Y.; Wu, Wanli; Hendrata, Siska; Huang, Yuhua; Wong, Jesse K.; Nair, Latha G.
PATENT ASSIGNEE(S): Schering Corporation, USA; Corvas International, Inc.
SOURCE: PCT Int. Appl., 633 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003062265	A2	20030731	WO 2003-US1430	20030116

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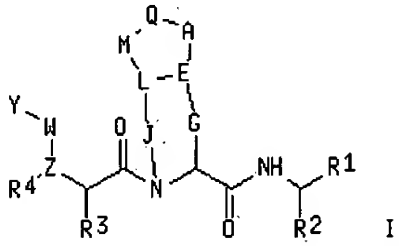
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-52386 A 20020118
OTHER SOURCE(S): MARPAT 139:149928
GI



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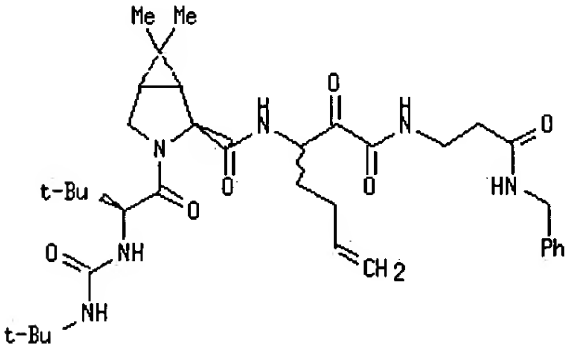


II

AB The invention discloses novel peptides I [Y is alkyl, alkylaryl, heteroalkyl, heteroaryl, aryl- or alkylheteroaryl, cycloalkyl, alkyloxy, alkylaryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkylarylamino, arylamino, heteroarylamino,

cycloalkylamino, or heterocycloalkylamino; R1 is acyl; Z is selected from O, N, CH or CR; R, R2-R4 are H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halo, (cycloalkyl)alkyl, or (heterocycloalkyl)alkyl; W, Q, G, J, L, M independently may be present or absent; W is CO, CS, C(:N-CN), or SO2; Q is CH, N, P, alkylidene, O, NR, S, or SO2; A is O, CH, alkylidene, NR, S, SO2, or a bond; E is CH, N, alkylidene, or a double bond; G is alkylidene; J is alkylidene, SO2, NH, NR, or O; L is CH, CR, O, S, or NR; M is O, NR, S, SO2, or alkylidene (with provisos)] which have HCV protease inhibitory activity as well as methods for prepg. such compds. In another embodiment, the invention discloses pharmaceutical compns. comprising such compds. as well as methods of using them to treat disorders assocd. with the HCV protease. Thus, peptide II was prepd. and showed Ki = 1-100 nM (category A) in the HCV continuous assay.

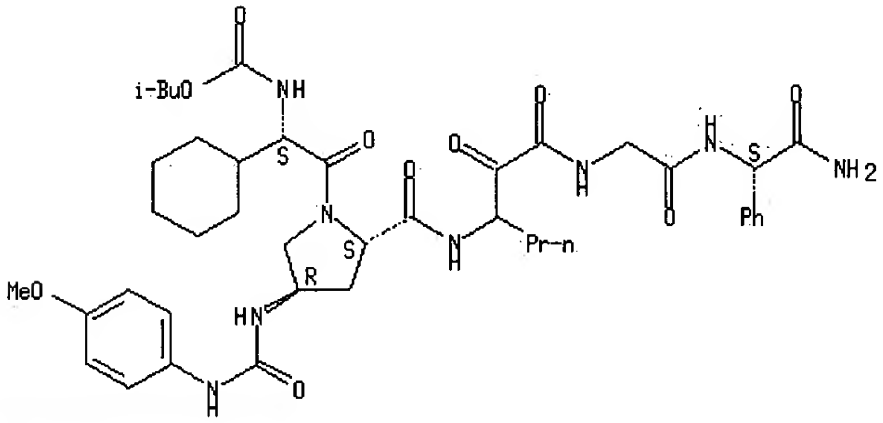
IT **394723-07-0P**

RL: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of peptides as NS3-serine protease inhibitors of hepatitis C virus)

RN 394723-07-0 HCAPLUS

CN Glycinamide, (2S)-2-cyclohexyl-N-[(2-methylpropoxy)carbonyl]glycyl-(4R)-4-[[[(4-methoxyphenyl)amino]carbonyl]amino]-L-prolyl-3-amino-2-oxohexanoylglycyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L24 ANSWER 6 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER:	2003:454318 HCAPLUS
DOCUMENT NUMBER:	139:36450
TITLE:	Preparation of 4-[(piperidylalkyl)ureido]quinolines, 4-[(pyrrolidylalkyl)ureido]quinolines, and analogs as urotensin II receptor antagonists
INVENTOR(S):	Aissaoui, Hamed; Binkert, Christoph; Clozel, Martine; Mathys, Boris; Mueller, Claus; Nayler, Oliver; Scherz, Michael; Velker, Joerg; Weller, Thomas
PATENT ASSIGNEE(S):	Actelion Pharmaceuticals Ltd., Switz.
SOURCE:	PCT Int. Appl., 139 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003048154	A1	20030612	WO 2002-EP13577	20021202

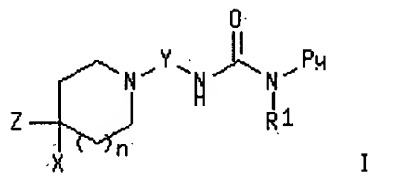
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 2001-EP14195 A 20011204

OTHER SOURCE(S): MARPAT 139:36450

GI



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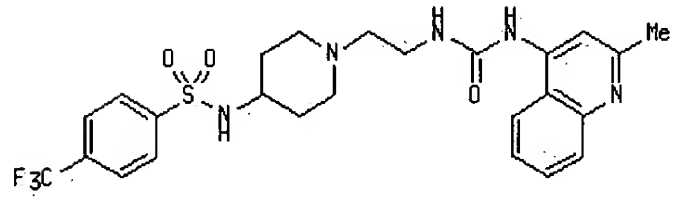
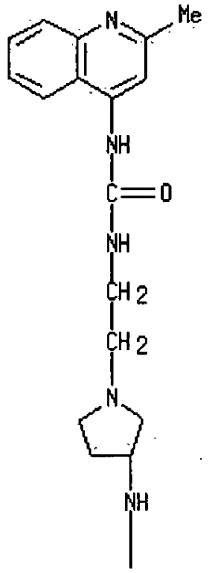


II

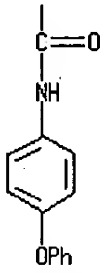
AB Title (pyridin-4-yl)urea derivs. and related compds. I [wherein Py = (un)substituted 2-NR2R3-pyridin-4-yl, quinolin-4-yl, (5,6,7,8-tetrahydro)[1,8]naphthyridin-4-yl, or 2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl; X = aryl(oxy), arylalkyl, (aryl)alkyl-SO2NR2, aryl-SO2NR2, (aryl)alkyl-CONR2, aryl-CONR2, (aryl)alkyl-NR3CONR2, aryl-NR3CONR2, aroyl, arylalkanoyl, (aryl)alkyl-NR2CO, aryl-NR2CO, etc.; Y = CR4R5(CH2)m or (CH2)mCR4R5; Z = H; or when X = aryl(alkyl), Z = H, OH, CO2H, aryl-CONR2, alkyl-NR2CO, or (aryl)alkyl-NR2CO; m = 1-2; n = 0-1; R1 = H or alkyl; R2 and R3 = independently H or (aryl)alkyl; or NR2R3 = piperidyl, pyrrolidinyl, or morpholinyl; R4 = H, (aryl)alkyl, or aryl; R5 = H or Me; or CR4R5 = carbocyclyl; and enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, solvates, or morphol. forms thereof] were prepd. as urotensin II receptor antagonists. For example, reaction of 4-amino-2-methylquinoline with 2-chloroethylisocyanate gave the urea. Substitution with piperidin-4-ylcarbamic acid tert-Bu ester, deprotection of the amine, and coupling with 4-trifluoromethylbenzenesulfonyl chloride provided II. Compds. of the invention inhibited binding of human [125I]-urotensin II to human-derived rhabdomyosarcoma cells in vitro with IC50 values ranging from 0.1 nM to 1000 nM. Thus, I are useful as active ingredients in pharmaceutical compns. for the treatment of vasoconstriction, proliferation, and a wide variety of other disease states assocd. with urotensin II regulation (no data).

IT **540767-32-6P**, 1-(2-Methylquinolin-4-yl)-3-[2-[3-[3-(4-phenoxyphenyl)ureido]pyrrolidin-1-yl]ethyl]urea
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(urotensin antagonist; prepn. of ureidoquinolines and analogs as urotensin II receptor antagonists for treatment of vasoconstriction, proliferation, and other disorders)
RN 540767-32-6 HCAPLUS
CN Urea, N-[1-[2-[[[(2-methyl-4-quinolinyl)amino]carbonyl]amino]ethyl]-3-pyrrolidinyl]-N'-(4-phenoxyphenyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 7 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

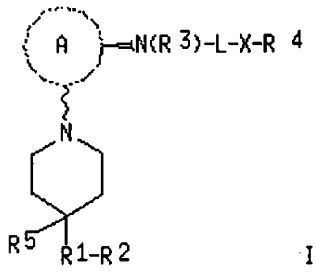
ACCESSION NUMBER: 2003:434550 HCAPLUS
DOCUMENT NUMBER: 139:22112
TITLE: Preparation of ureido and related piperidines as CCR3 receptor antagonists for treating asthma
INVENTOR(S): Du Bois, Daisy Joe; Kertesz, Denis John; Sjogren, Eric Brian; Smith, David Bernard; Wang, Beihan
PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.

SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003045937	A1	20030605	WO 2002-EP13218	20021125
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003229121	A1	20031211	US 2002-307130	20021129

PRIORITY APPLN. INFO.: US 2001-334653P P 20011130
US 2001-334655P P 20011130
US 2001-334819P P 20011130

OTHER SOURCE(S): MARPAT 139:22112
GI



I

AB The present invention relates to N-ureido-piperidines (shown as I; variables defined below; e.g. trans-1-[2-[4-(4-chlorobenzyl)piperidin-1-yl]cyclohexyl]-3-(3,4,5-trimethoxyphenyl)urea). The compds. are useful as CCR3 receptor antagonists by blocking the ability of the CCR-3 receptor to bind RANTES, MCP-3 and eotaxin and thereby preventing the recruitment of eosinophils, and therefore, may be used for treatment of CCR3 mediated diseases such as asthma. Five pharmaceutical formulations are described. Seven example prepns. of intermediates and 31 of I are included. For example, trans-1-[2-[4-(4-chlorobenzyl)piperidin-1-yl]cyclohexyl]-3-(3,4,5-trimethoxyphenyl)urea was prepd. in 55% yield from [trans-2-[4-(4-chlorobenzyl)piperidin-1-yl]cyclohexyl]amine (56 mg, 0.18 mmol) and 5-isocyanato-1,2,3-trimethoxybenzene in CH2Cl2; [trans-2-[4-(4-chlorobenzyl)piperidin-1-yl]cyclohexyl]amine was prepd. in 2 steps starting from 4-(4-chlorobenzyl)piperidine and 7-oxabicyclo[4.1.0]heptane via intermediate trans-2-[4-(4-chlorobenzyl)piperidin-1-yl]cyclohexanol with yields of 88 and 67%. IC50 values for inhibiting the binding of 125I eotaxin to CCR-3 L1.2 transfectant cells were detd. for 10 examples of I, e.g. 0.0185 μM for trans-N-[3-[3-[2-[4-(4-Chlorobenzyl)piperidin-1-yl]cyclopentyl]ureido]phenyl]acetamide. For I: R1 is (C1-C2)alkylene; R2

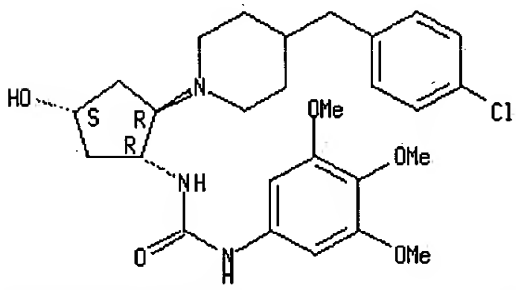
is (un)substituted phenyl; R3 is H, C1-6 alkyl, acyl, aryl, or aryl C1-6 alkyl; ring A is a C3-7 cycloalkyl, heterocyclyl, or (un)substituted phenyl; L is -C(O)-, -C(S)-, -SO2-, -C(O)N(Ra)-, -C(S)N(Ra)-, -SO2N(Ra)-, -C(O)O-, -C(S)-O-, -S(O)2O-; where Ra is H, C1-6 alkyl, acyl, aryl, aryl C1-6 alkyl, C1-6 alkoxycarbonyl, or benzyloxycarbonyl; X is absent, -(CR'R'')O-, -(CR'R'')S-, -(CR'R'')NRb- or C1-6 alkylene; where R' and R'' = H or C1-6 alkyl, and Rb is H or C1-6 alkyl; R4 is aryl or heteroaryl; and R5 is H or C1-6 alkyl; provided that when R1 is -CH2-, R2 is Ph, R3 is H, R5 is H, A is Ph, L is -C(O)NH- and X is absent, then R4 is not 2,5-difluorophenyl.

IT **538371-04-9P**, (±)-1-[(1R,2R,4S)-2-[4-(4-Chlorobenzyl)piperidin-1-yl]-4-hydroxycyclopentyl]-3-(3,4,5-trimethoxyphenyl)urea
RL: DGN (Diagnostic use); PAC (Pharmacological activity); RCT (Reactant); **THU (Therapeutic use)**; **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate and diagnosis agent; prepn. of ureido and related piperidines as CCR3 receptor antagonists for treating asthma)

RN 538371-04-9 HCAPLUS

CN Urea, N-[(1R,2R,4S)-2-[4-[(4-chlorophenyl)methyl]-1-piperidinyl]-4-hydroxycyclopentyl]-N'-(3,4,5-trimethoxyphenyl)-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 8 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:434371 HCAPLUS
DOCUMENT NUMBER: 139:22109
TITLE: Preparation of piperazinyl carboxamides, sulfonamides, ureas and related compounds as CCR3 receptor antagonists for treating asthma
INVENTOR(S): Du Bois, Daisy Joe; Kertesz, Denis John; Sjogren, Eric Brian; Smith, David Bernard; Wang, Beihan
PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003045393	A1	20030605	WO 2002-EP13217	20021125

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

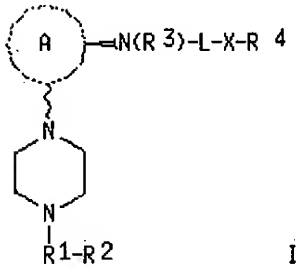
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG

US 2003176441	A1	20030918	US 2002-307159	20021129
US 2003229121	A1	20031211	US 2002-307130	20021129

PRIORITY APPLN. INFO.:

US 2001-334655P	P	20011130
US 2001-334653P	P	20011130
US 2001-334819P	P	20011130

OTHER SOURCE(S): MARPAT 139:22109
GI



I

AB The present invention relates to piperazinyl carboxamides, sulfonamides, ureas and related compds. (shown as I; variables defined below; e.g. trans-1-[4-[4-(4-chlorobenzyl)piperazin-1-yl]tetrahydrofuran-3-yl]-3-(3,4,5-trimethoxyphenyl)urea dihydrochloride). The compds. are useful as CCR3 receptor antagonists by blocking the ability of the CCR-3 receptor to bind RANTES, MCP-3 and eotaxin and thereby preventing the recruitment of eosinophils, and therefore, may be used for treatment of CCR3 mediated diseases such as asthma or for diagnosis. Five pharmaceutical formulations are described. Seven example prepns. of I are included. For example, the above compd. was prepd. in 77% yield from trans-4-[4-(4-chlorobenzyl)piperazin-1-yl]tetrahydrofuran-3-ylamine (0.41 mmol) and 5-isocyanato-1,2,3-trimethoxybenzene (0.50 mmol) in CH2Cl2; prepn. of the amine is also described. IC50 values for inhibiting the binding of 125I eotaxin to CCR-3 L1.2 transfectant cells were detd. for 4 examples of I, e.g. 0.1099 μM for the above example. For I: R1 is (C1-C2)alkylene; R2 is (un)substituted phenyl; R3 is H, C1-6 alkyl, acyl, aryl, or aryl C1-6-alkyl; ring A is a C3-7 cycloalkyl, heterocyclyl, or (un)substituted phenyl; L is -C(O)-, -C(S)-, -SO2-, -C(O)N(Ra)-, -C(S)N(Ra)-, -SO2N(Ra)-, -C(O)O-, -C(S)O-, -S(O)2O-; where Ra is H, C1-6 alkyl, acyl, aryl, aryl C1-6 alkyl, C1-6-alkoxycarbonyl, or benzyloxycarbonyl. X is absent, -(CR'R'')O-, -(CR'R'')S-, -(CR'R'')NRb- or C1-6 alkylene; where R' and R'' = H or C1-6-alkyl, and Rb is H or C1-6 alkyl; R4 is aryl or heteroaryl; provided that I is not 1-[2-[4-(3,4-dichlorobenzyl)piperazin-1-yl]cyclohexyl]-3-(3-methoxyphenyl)urea; and provided that when ring A is Ph or cyclohexyl, then R2 is substituted Ph.

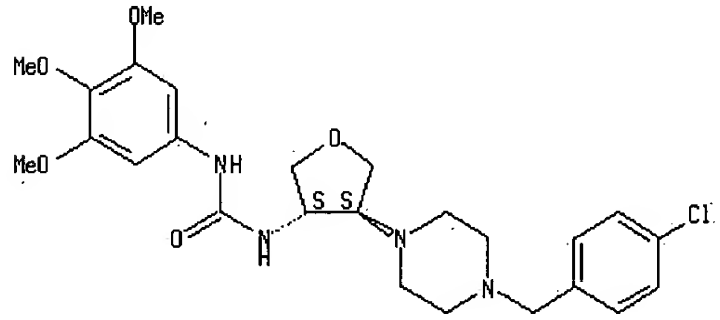
IT **538342-64-2P**, trans-1-[4-[4-(4-Chlorobenzyl)piperazin-1-yl]tetrahydrofuran-3-yl]-3-(3,4,5-trimethoxyphenyl)urea dihydrochloride
RL: DGN (Diagnostic use); PAC (Pharmacological activity); SPN (Synthetic

preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; prepn. of piperazinyl carboxamides, sulfonamides, ureas and related compds. as CCR3 receptor antagonists for treating/diagnosing asthma)

RN 538342-64-2 HCAPLUS

CN Urea, N-[(3R,4R)-4-[4-[(4-chlorophenyl)methyl]-1-piperazinyl]tetrahydro-3-furanyl]-N'-(3,4,5-trimethoxyphenyl)-, dihydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



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REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 9 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:282524 HCAPLUS
DOCUMENT NUMBER: 138:304064
TITLE: Preparation of phenylurea derivatives as vanilloid receptor agonists
INVENTOR(S): Matsumoto, Takahiro; Yamamoto, Masataka; Nagabukuro, Hiroshi; Mochizuki, Manabu
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 293 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003029199	A1	20030410	WO 2002-JP9995	20020927
WO 2003029199	C2	20030925		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,

PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2001-300564 A 20010928

OTHER SOURCE(S): MARPAT 138:304064

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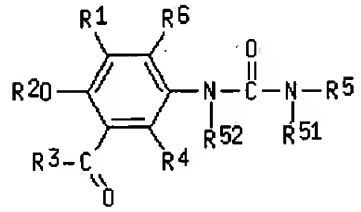


I

AB The title compds. I [R1, R4 and R6 are each independently hydrogen, halogeno, or hydrocarbyl; R2 is hydrocarbyl or a heterocyclic group; R3 is hydrocarbyl, etc.; R5 is hydrocarbyl or a heterocyclic group (except quinolyl) and R51 is hydrogen or hydrocarbyl, or R5 and R51 together with the nitrogen atom adjacent thereto may form a ring; and R52 is hydrogen or hydrocarbyl] are prepd. I are useful for the treatment of pain, urinary incontinence, etc. In a tail flick test using mice, one compd. of this invention showed a min. ED of 1 mg/kg.

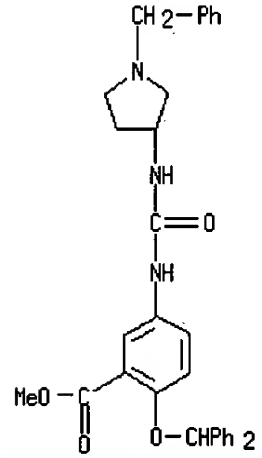
IT **508214-27-5P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of phenylurea derivs. as vanilloid receptor agonists)

RN 508214-27-5 HCAPLUS

CN Benzoic acid, 2-(diphenylmethoxy)-5-[[[[1-(phenylmethyl)-3-pyrrolidinyl]amino]carbonyl]amino]-, methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 10 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:221645 HCAPLUS

DOCUMENT NUMBER: 138:254963

TITLE: Preparation of acylaminocyclopentaneamines as CCR-3 chemokine receptor antagonists that inhibit eosinophilic recruitment by chemokines.

INVENTOR(S): Du Bois, Daisy Joe
PATENT ASSIGNEE(S): F. Hoffmann-La Roche AG, Switz.
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003022799	A1	20030320	WO 2002-EP9934	20020905
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003119885	A1	20030626	US 2002-242610	20020912

PRIORITY APPLN. INFO.: US 2001-318992P P 20010913
OTHER SOURCE(S): MARPAT 138:254963
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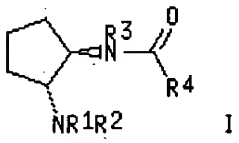


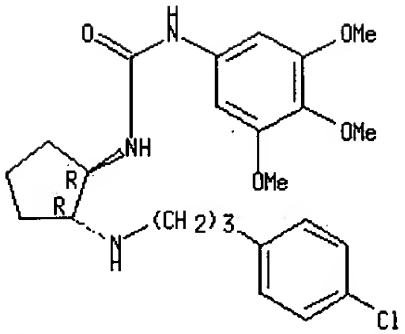
I

AB Title compds. [I; R1 = H, alkyl; R2 = aralkyl; R3 = H, alkyl, acyl, aryl, aralkyl; R4 = WXYZ; W = null, alkylene; X = null, CO, O, S, SO, SO2, NRa; Ra = H, alkyl, acyl, aryl, aralkyl, alkoxycarbonyl, benzyloxycarbonyl; Y = arylene, heteroarylene; Z = H, aryl, heteroaryl, aryloxy, heteroaryloxy, aralkyl, heteroaralkyl], were prepd. Thus, reaction of trans-N-[2-(4-chlorophenyl)ethyl]-N-methylcyclopentane-1,2-diamine and 5-isocyanato-1,2,3-trimethoxybenzene reacted to give trans-1-[2-[[2-(4-chlorophenyl)ethyl]methylamino]cyclopentyl]-3-(3,4,5-trimethoxyphenyl)urea hydrochloride. The latter inhibited [125I]eotaxin binding to CCR-3 L1.2 transfectant cells with IC50 = 5.4 μM.

IT 502522-59-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of acylaminocyclopentaneamines as CCR-3 receptor antagonists that inhibit eosinophilic recruitment by chemokines)

RN 502522-59-0 HCAPLUS
CN Urea, N-[(1R,2R)-2-[[3-(4-chlorophenyl)propyl]amino]cyclopentyl]-N'-(3,4,5-trimethoxyphenyl)-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 11 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

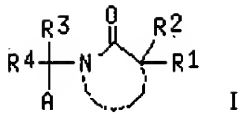
Full Text | Citing References

ACCESSION NUMBER: 2002:444499 HCAPLUS
DOCUMENT NUMBER: 137:33207
TITLE: Preparation of novel N-substituted-γ,γ-trisubstituted lactam derivatives as matrix metalloproteinase inhibitors
INVENTOR(S): Duan, Jingwu; DeCicco, Carl P.; Wasserman, Zelda R.; Maduskuie, Thomas P., Jr.
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 119 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6403632	B1	20020611	US 2000-516709	20000301
US 2003134827	A1	20030717	US 2002-96619	20020312
US 6610731	B2	20030826		

PRIORITY APPLN. INFO.: US 1997-62418P P 19971003
US 1998-165747 A3 19981002
US 2000-516709 A3 20000301

OTHER SOURCE(S): MARPAT 137:33207
GI



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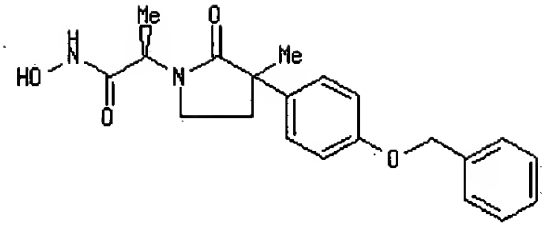


II

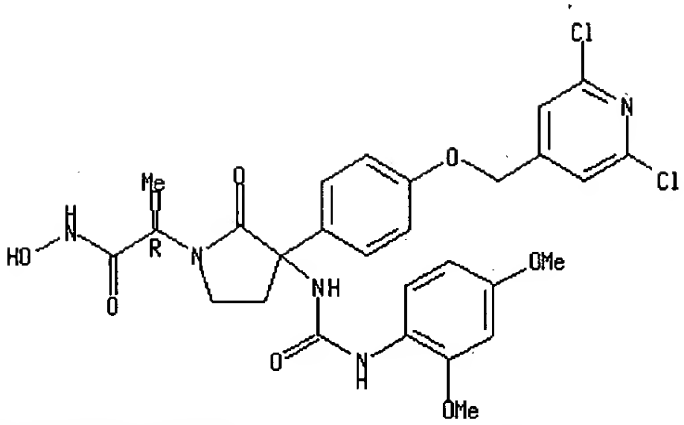
AB Title compds. [I; A is selected from COOH, CH2COOH, CONHOH, SH, CH2SH, PO(OH)2, etc.; ring B is a 4-8 membered cyclic amide contg. 0-3 heteroatoms from O, N, and S, etc.; R1 is phenylmethoxyphenyl, phenoxyphenyl, etc.; R2 is H, CH3, Et, i-Pr, etc.; R1-R2 combine to form heterocyclic; R3 is H, alkylene, heterocyclic, etc.; R4 is H, alkylene, etc.; R3-R4 combine to form heterocyclic], stereoisomer, and pharmaceutically acceptable salt thereof are prepd. as useful metalloprotease inhibitors. For instance, 4-benzyloxyphenyl acetate was sequentially alkylated (THF, NaHMDS) with MeI and allyl bromide to afford the α,α-bis(alkylated) deriv. which was converted to the aldehyde (CH2Cl2, O3) and was subsequently reacted with D-alanine Me ester hydrochloride and Zn° in HOAc to yield the lactam ester. This intermediate was treated with hydroxylamine to give hydroxamic acid II.

IT **223403-48-3P**, 1-Pyrrolidineacetamide, 3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-3-[[[(2,4-dimethoxyphenyl)amino]carbonyl]amino]-N-hydroxy-α-methyl-2-oxo-, (αR)-
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(N-γ,γ-trisubstituted lactam derivs. as MMP-3/aggrecanase inhibitors)

RN 223403-48-3 HCAPLUS

CN 1-Pyrrolidineacetamide, 3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-3-[[[(2,4-dimethoxyphenyl)amino]carbonyl]amino]-N-hydroxy-α-methyl-2-oxo-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 12 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

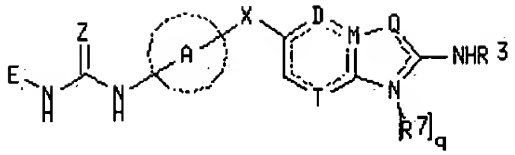
ACCESSION NUMBER: 2002:428885 HCAPLUS
DOCUMENT NUMBER: 137:6179
TITLE: Preparation of benzimidazoles as TIE-2 and/or VEGFR2 inhibitors
INVENTOR(S): Cheung, Mui; Harris, Philip Anthony; Hasegawa, Masaichi; Ida, Satoru; Kano, Kazuya; Nishigaki, Naohiko; Sato, Hideyuki; Veal, James Martin; Washio, Yoshiaki; West, Rob I.
PATENT ASSIGNEE(S): Glaxo Group Limited, UK; Glaxosmithkline K.K.
SOURCE: PCT Int. Appl., 217 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002044156	A2	20020606	WO 2001-US44553	20011128
WO 2002044156	A3	20021017		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002032439	A5	20020611	AU 2002-32439	20011128
EP 1341771	A2	20030910	EP 2001-991963	20011128
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.:

US 2000-253868P	P	20001129
US 2001-310939P	P	20010808
WO 2001-US44553	W	20011128

OTHER SOURCE(S): MARPAT 137:6179
GI



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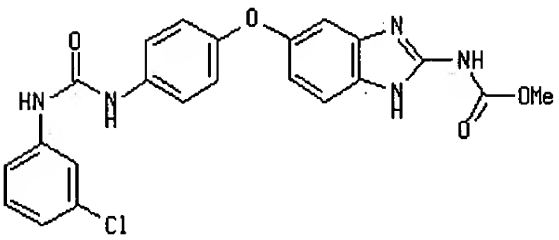


II

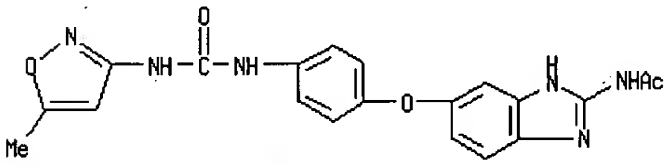
AB The title compds. [I; E = (un)substituted aryl, heteroaryl; A = aryl, heteroaryl, heterocyclyl; X = S, O, SO2, SO, CH2, CHOH, CO; Z = O, S; p = 0-1; q = 0-1; D = CH, T = CR8, M = C and Q = NT7p, wherein p = 0 and q = 1; or D = CH, T = CR8, M = C and Q = NR7p, wherein p =1 and q = 0, or D = CH, T = CR8, M = C and Q = S or O, wherein q = 0; or D = N, T = CR8, M = C and Q = NR7p, wherein either p or q = 0 and the other = 1; or D = CH, T = N, M = C and Q = NR7p, wherein either p or q = 0 and the other = 1; or D = CH, T = CR8, M = N and Q = CH, wherein q = 0; R1 = alkyl, haloalkyl, aryl, etc.; R2 = H, alkyl, aryl, etc.; R3 = alkylene or alkylene substituted by oxo, and is linked together with N atom to which it is attached and to one of the benzimidazole N atoms to form a heterocyclic compd. fused to the benzimidazole; R7 = H, alkyl, etc.; R8 = H, halo] and their salts, useful in the treatment of hyperproliferative diseases, were prepd. Thus, reacting Me [5-(4-aminophenoxy)-1H-benzimidazol-2-yl]carbamate (prepn. given) with 3-chlorophenyl isocyanate in THF afforded 69% II which showed pIC50 of > 7.0 in TIE-2 and VEGFR2 enzyme assays.

IT **433225-41-3P**

RL: CPN (Combinatorial preparation); PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); CMBI (Combinatorial study); PREP (Preparation); USES (Uses)
(prepn. of benzimidazoles as TIE-2 and/or VEGFR2 inhibitors)

RN 433225-41-3 HCAPLUS

CN Acetamide, N-[5-[4-[[[(5-methyl-3-isoxazolyl)amino]carbonyl]amino]phenoxy]-1H-benzimidazol-2-yl]- (9CI) (CA INDEX NAME)



L24 ANSWER 13 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:90074 HCAPLUS
DOCUMENT NUMBER: 136:151440
TITLE: Preparation of novel peptides as NS3-serine protease inhibitors of hepatitis C virus
INVENTOR(S): Saksena, Anil K.; Girijavallabhan, Viyyoor Moopil; Lovey, Raymond G.; Jao, Edwin E.; Bennett, Frank; McCormick, Jinping; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Liu, Yi-Tsung; Arasappan, Ashok;

Parekh, Tejal; Pinto, Patrick A.; Njoroge, F. George; Ganguly, Ashit K.; Brunck, Terence K.; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita

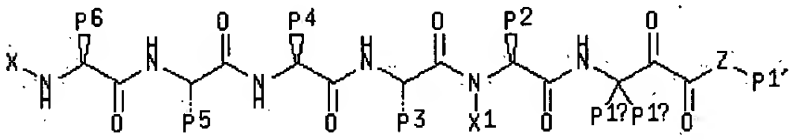
PATENT ASSIGNEE(S): Schering Corporation, USA; Corvas International, Inc.
SOURCE: PCT Int. Appl., 197 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002008256	A2	20020131	WO 2001-US22826	20010719
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003036501	A1	20030220	US 2001-909062	20010719
EP 1301528	A2	20030416	EP 2001-959046	20010719
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-220109P P 20000721
WO 2001-US22826 W 20010719

OTHER SOURCE(S): MARPAT 136:151440

GI



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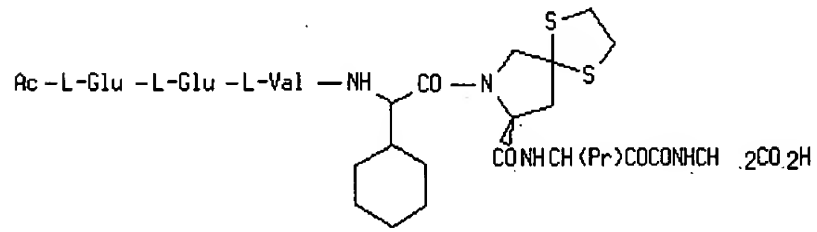


II

AB Novel peptides I [Z = O, NH or substituted imino; X = (un)substituted alkylsulfonyl, heterocyclylsulfonyl, heterocyclylalkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, heterocycloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkyaminocarbonyl, heterocyclylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl; X1 = H, alkyl, arylmethyl; P1a, P1b, P2-P6 = H, (un)substituted alkyl, alkenyl, cycloalkyl,

heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl; P1a and P1b may optionally be joined to each other to form a spirocyclic or spiroheterocyclic ring contg. 0-6 oxygen, nitrogen, sulfur, or phosphorus atoms; P1' = H, (un)substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl] having HCV protease inhibitory activity are disclosed. Thus, peptide II was prepd. via peptide coupling in soln. and showed Ki = 1-100 nM for inhibition of HCV protease.

IT **393523-09-6P**

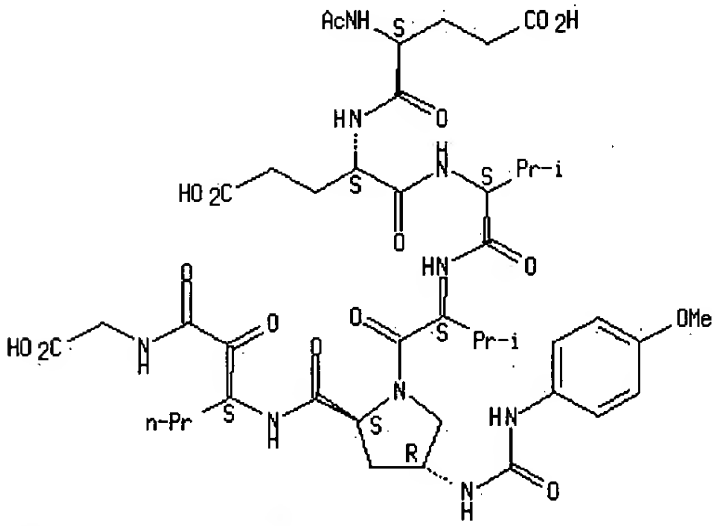
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of novel peptides as NS3-serine protease inhibitors of hepatitis C virus)

RN 393523-09-6 HCAPLUS

CN Glycine, N-acetyl-L-α-glutamyl-L-α-glutamyl-L-valyl-L-valyl-(4R)-4-[[[(4-methoxyphenyl)amino]carbonyl]amino]-L-prolyl-(3S)-3-amino-2-oxohexanoyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L24 ANSWER 14 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

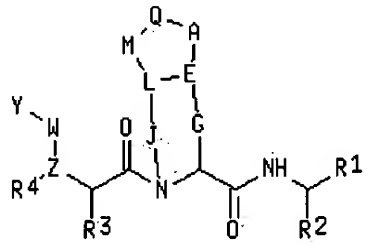
ACCESSION NUMBER: 2002:90062 HCAPLUS
DOCUMENT NUMBER: 136:167698
TITLE: Preparation of peptides as NS3-serine protease inhibitors of hepatitis C virus
INVENTOR(S): Saksena, Anil K.; Girijavallabhan, Viyyoor Moopil; Lovey, Raymond G.; Jao, Edwin E.; Bennett, Frank; McCormick, Jinping L.; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Chan, Tin-Yau; Liu, Yi-Tsung; Zhu, Zhaoning; Njoroge, F. George; Arasappan, Ashok; Parekh, Tejal N.; Ganguly, Ashit K.; Chen, Kevin X.; Venkatraman, Srikanth; Vaccaro, Henry A.; Pinto, Patrick A.; Santhanam, Bama; Wu, Wanli; Hendrata, Siska; Huang, Yuhua; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita; Tamura, Susan Y.
PATENT ASSIGNEE(S): Schering Corporation, USA; Corvas International, Inc.
SOURCE: PCT Int. Appl., 536 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002008244	A2	20020131	WO 2001-US22678	20010719
WO 2002008244	A3	20030619		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001076988	A5	20020205	AU 2001-76988	20010719
BR 2001012540	A	20030624	BR 2001-12540	20010719
EP 1385870	A2	20040204	EP 2001-954764	20010719
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004504404	T2	20040212	JP 2002-514149	20010719
NO 2003000272	A	20030321	NO 2003-272	20030120

PRIORITY APPLN. INFO.: US 2000-220108P P 20000721
WO 2001-US22678 W 20010719

OTHER SOURCE(S): MARPAT 136:167698
GI



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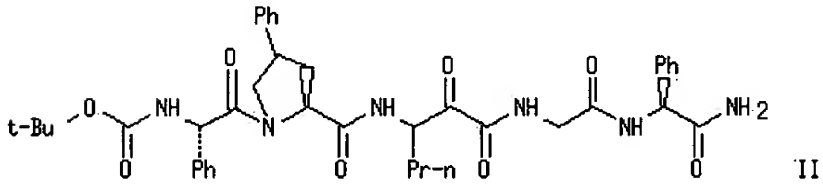


II

AB Peptides I were prepd. wherein Y is alkyl, alkyl-aryl, heteroaryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkylheteroaryl, cycloalkyl, alkyloxy, alkylaryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy,, alkylamino, arylamino, alkylarylamino, arylamino, heteroarylamino, cycloalkylamino and heterocycloalkylamino; R1 is acyl, borate; Z is selected from O, N, CH or CR; W, Q, G, J, L, M independently maybe present or absent; W is C=O, C=S, C(=N-CN), or SO; Q is CH, N, P, alkylidene, O, amine,S, or SO; A is O, CH, alkylidene, amine, S, SO or bond; E is CH, N, alkylidene, or double bond; G is alkylidene; J is

alkylidene, SO, NH, NR, O; L is CH, alkylidene, O, S or NR; M is O, NR,S, SO, alkylidene; p is 0 to 6; and R-R4 are independently selected from the group consisting of H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, which have HCV protease inhibitory activity as well as methods for prepg. such compds. In another embodiment, the invention discloses pharmaceutical compns. comprising such compds. as well as methods of using them to treat disorders assocd. with the HCV protease. Thus peptide II was prepd. and tested as antiviral agent and NS3-serine protease inhibitors of hepatitis C virus with Ki ranges in category A = 1-100 nM; category B = 101-1,000 nM; category C > 1000 nM. Also disclosed is the use of I for the manuf. of a medicament for treating HCV, AIDS, and related disorders.

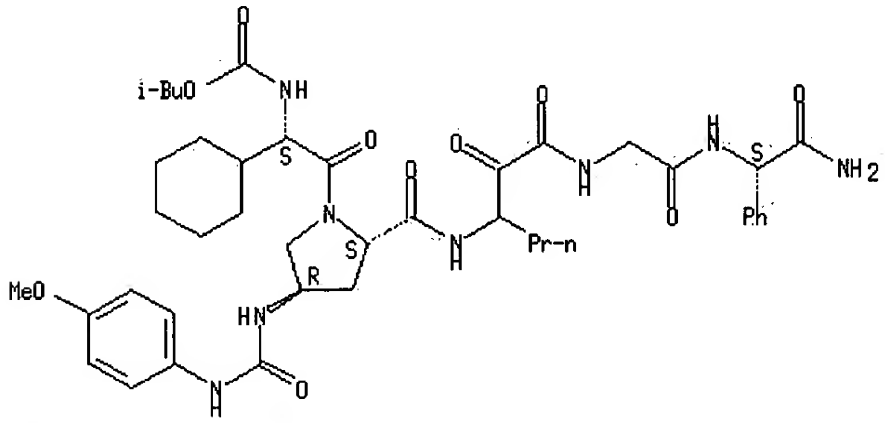
IT **394723-07-0P**

RL: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of peptides as NS3-serine protease inhibitors of hepatitis C virus)

RN 394723-07-0 HCAPLUS

CN Glycinamide, (2S)-2-cyclohexyl-N-[(2-methylpropoxy)carbonyl]glycyl-(4R)-4-[[[(4-methoxyphenyl)amino]carbonyl]amino]-L-prolyl-3-amino-2-oxohexanoylglycyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L24 ANSWER 15 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:923806 HCAPLUS
DOCUMENT NUMBER: 136:53742
TITLE: Preparation of 5H-isoxazolo[4,3-c]quinolin-4-ones as MRP1 inhibitors
INVENTOR(S): Lander, Peter Ambrose; Wang, Qiuping; Vepachedu, Sreenivasarao
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

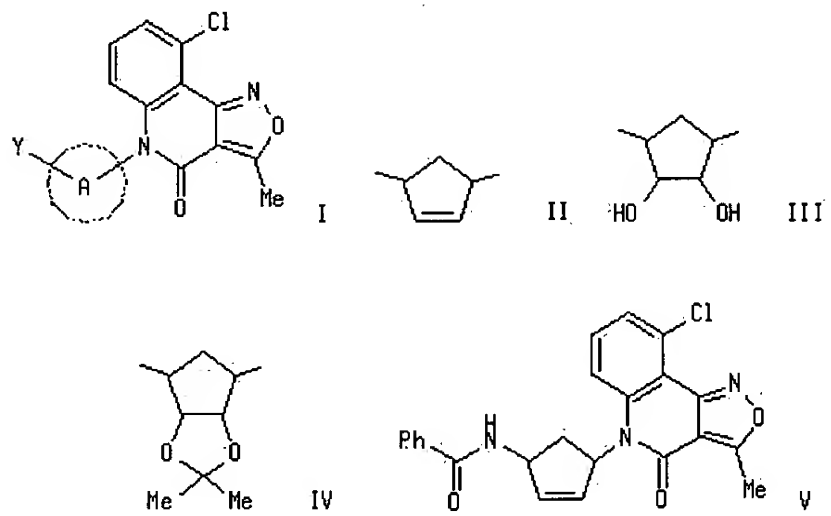
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2001096346	A1	20011220	WO 2001-US16475	20010531	
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
EP 1301518	A1	20030416	EP 2001-941546	20010531	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
US 2003216425	A1	20031120	US 2003-296481	20030416	
US 6673809	B2	20040106			

PRIORITY APPLN. INFO.: US 2000-211430P P 20000614
WO 2001-US16475 W 20010531

OTHER SOURCE(S): MARPAT 136:53742

GI

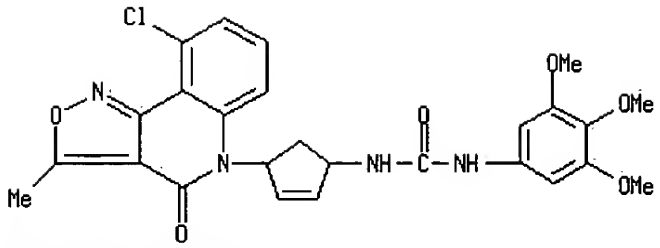


AB The title compds. [I; A = II-IV; Y = ECOR1; ENR2R3; E = a bond, CH2; R1 = H, alkyl, cycloalkyl, etc.; R2 = H, alkyl, alkylaryl, aryl; R3 = H, alkyl, alkoxy, etc.], useful for inhibiting resistant neoplasms where the resistance is conferred in part or in total by MRP1 (no data), were prepd. Thus, reacting 5-(4-aminocyclopent-2-enyl)-9-chloro-3-methyl-5H-isoxazolo[4,3-c]quinolin-4-one (prepn. given) with benzoyl chloride in the presence of Et3N in CH2Cl2 afforded 55% V.

IT **381688-83-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 5H-isoxazolo[4,3-c]quinolin-4-ones as MRP1 inhibitors)

RN 381688-83-1 HCAPLUS

CN Urea, N-[4-(9-chloro-3-methyl-4-oxoisoxazolo[4,3-c]quinolin-5(4H)-yl)-2-cyclopenten-1-yl]-N'-(3,4,5-trimethoxyphenyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 16 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:693247 HCAPLUS
DOCUMENT NUMBER: 135:257156
TITLE: Preparation of sulfonamido substituted phenyl heteroaryl ureas as IL-8 receptor antagonists
INVENTOR(S): Widdowson, Katherine L.; Jin, Qi
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001068568	A2	20010920	WO 2001-US7746	20010309
WO 2001068568	A3	20020321		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001045606	A5	20010924	AU 2001-45606	20010309
EP 1261336	A2	20021204	EP 2001-918542	20010309
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003535820	T2	20031202	JP 2001-567669	20010309
NO 2002004193	A	20020903	NO 2002-4193	20020903
US 2003055286	A1	20030320	US 2002-220772	20020905
US 6608077	B2	20030819		

PRIORITY APPLN. INFO.: US 2000-188410P P 20000310
WO 2001-US7746 W 20010309

OTHER SOURCE(S): MARPAT 135:257156
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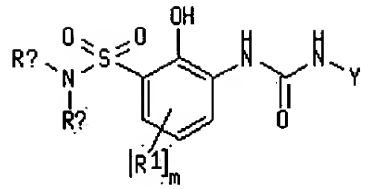


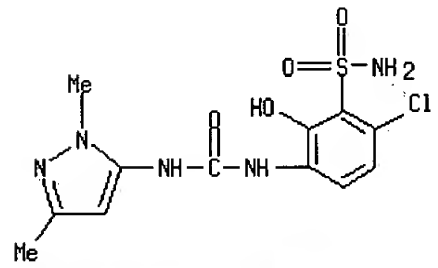
I

AB The title compds. [I; Rb = H, OH, aryl, etc.; m = 1-3; R1 = H, halo, NO2, etc.; Y = furyl, thiophenyl, pyridyl, etc.], useful in the treatment of disease states mediated by the chemokine, Interleukin-8 (IL-8), were prepd. Thus, reacting 3-amino-6-chloro-2-hydroxybenzenesulfonamide with 2-(azidocarbonyl)pyridine (prepns. given) in DMF afforded 62% I [Rb = H; R1 = 4-Cl; Y = 2-pyridyl]. The IL-8, and GRO-α chemokine effects of compds. I were detd. by in vitro assay (IC50 < 30 μM).

IT 361392-27-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of sulfonamido substituted Ph heteroaryl ureas as IL-8 receptor antagonists)

RN 361392-27-0 HCAPLUS

CN Benzenesulfonamide, 6-chloro-3-[[[(1,3-dimethyl-1H-pyrazol-5-yl)amino]carbonyl]amino]-2-hydroxy- (9CI) (CA INDEX NAME)



L24 ANSWER 17 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:693081 HCAPLUS
DOCUMENT NUMBER: 135:257046
TITLE: Preparation of sulfonamido substituted diphenyl ureas as IL-8 receptor antagonists
INVENTOR(S): Widdowson, Katherine L.; Jin, Qi
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001068084	A1	20010920	WO 2001-US8672	20010316

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,

YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1263427	A1	20021211	EP 2001-924195	20010316
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003526664	T2	20030909	JP 2001-566648	20010316
BG 107013	A	20030530	BG 2002-107013	20020820
US 2003078250	A1	20030424	US 2002-220989	20020906
US 6664259	B2	20031216		
NO 2002004367	A	20021022	NO 2002-4367	20020912

PRIORITY APPLN. INFO.: US 2000-189848P P 20000316
WO 2001-US8672 W 20010316

OTHER SOURCE(S): MARPAT 135:257046

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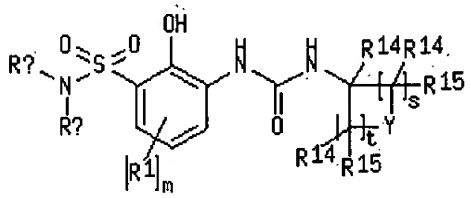


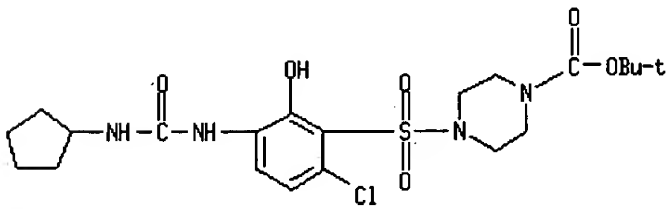
I

AB The title compds. [I; Rb = H, OH, aryl, etc.; m = 1-3; t = 0-2; s = 1-3; R1 = H, halo, NO2, etc.; Y = O, CO, NR14, etc.; R14, R15 = H, alkyl, ORa (Ra = alkyl, aryl, heteroaryl, etc.)] and their pharmaceutically acceptable salts, useful in the treatment of disease states mediated by the chemokine, Interleukin-8 (IL-8), were prepd. Thus, reacting 3-amino-6-chloro-2-hydroxybenzenesulfonamide (prepn. given) with cyclohexyl isocyanate in DMF afforded 52% I [Rb = H; R1 = 4-Cl; R14, R15 = H; t, s = 2; Y = CH2]. The IL-8, and GRO-α chemokine inhibitory effects of compds. I were detd. by in vitro assay (data given).

IT **361391-80-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); **THU (Therapeutic use)**; **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of sulfonamido substituted di-Ph ureas as IL-8 receptor antagonists)

RN 361391-80-2 HCAPLUS

CN 1-Piperazinecarboxylic acid, 4-[[6-chloro-3-[[(cyclopentylamino)carbonyl]amino]-2-hydroxyphenyl]sulfonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 18 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:489404 HCAPLUS
DOCUMENT NUMBER: 135:76901
TITLE: Preparation of quinazoline and quinoline derivatives as remedies for diseases mediated by autophosphorylation of PDGF receptors
INVENTOR(S): Ueno, Kimihisa; Ogawa, Akira; Ohta, Yoshihisa; Nomoto, Yuji; Takasaki, Kotaro; Kusaka, Hideaki; Yano, Hiroshi; Suzuki, Chiharu; Nakanishi, Satoshi
PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan
SOURCE: PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047931 A1		20010705	WO 2000-JP9160	20001222

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR

PRIORITY APPLN. INFO.: JP 1999-366313 19991224
OTHER SOURCE(S): MARPAT 135:76901
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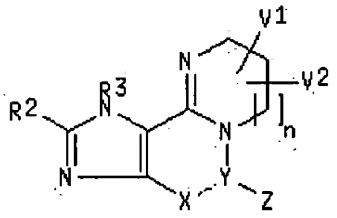

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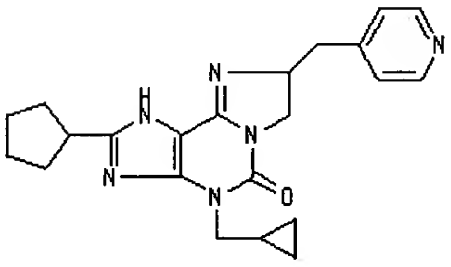


II

AB Title compds. [I; X = N, CH; R3, R4, R5, R6 independently = H, Cl, F, CH3, CH3O, NO2; A = 4-CH3C6H4CH2OCONH, 3-ClC6H4CH(CH3)OCONH, 4-FC6H4CH2OCONH, 2-ClC6H4CH(CH3)OCONH, 2-ClC6H4CH2CH2CH2OCONH, 4-CF3C6H4CH2OCONH,CH3(CH2)5OCONH, (CH3CH2)2N(CH2)3NHCSNH, YNHCONH, 4-ClC6H4O(CH2)2S, 4-ClC6H4(CH2)2NH, 3-BrC6H4CONHCSNH, C6H5COO, OH, OCH2COOCH3, OCH2COOH; Y = heterocycle, heterocyclylalkyl] and

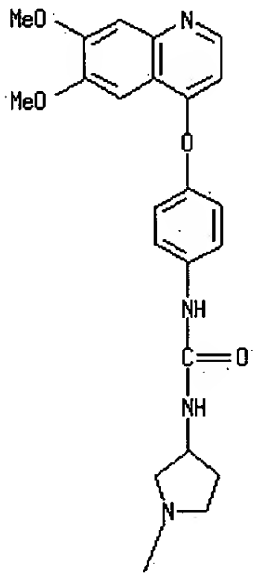
pharmaceutically acceptable salts are prepd. as remedies for diseases mediated by autophosphorylation of PDGF receptors. Thus, the title claimed compd. II was prepd. and biol. tested.

IT 347155-22-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of quinazolines and quinolines as remedies for diseases mediated by autophosphorylation of PDGF receptors)

RN 347155-22-0 HCAPLUS

CN Urea, N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-[1-(phenylmethyl)-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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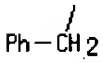

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 19 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:489372 HCAPLUS
DOCUMENT NUMBER: 135:92649
TITLE: Preparation of quinazoline and quinoline derivatives as remedies for diseases mediated by autophosphorylation of PDGF receptors
INVENTOR(S): Sakai, Teruyuki; Senga, Teruhumi; Furuta, Takayuki; Miwa, Atushi
PATENT ASSIGNEE(S): Kirin Beer Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 1068 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047890	A1	20010705	WO 2000-JP9157	20001222
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001022232	A5	20010709	AU 2001-22232	20001222
EP 1243582	A1	20020925	EP 2000-985844	20001222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.:			
JP 1999-377486	A	19991224	
JP 1999-374494	A	19991228	
JP 2000-177790	A	20000614	
WO 2000-JP9157	W	20001222	

OTHER SOURCE(S): MARPAT 135:92649

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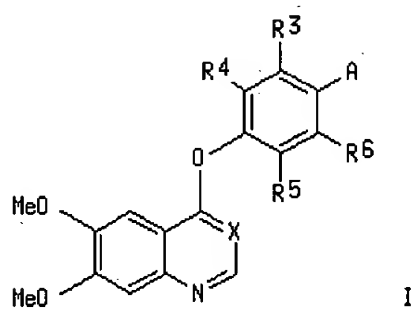

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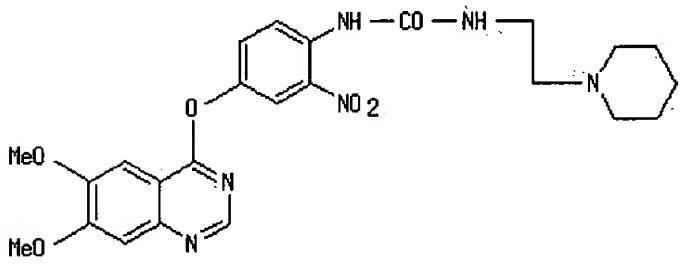
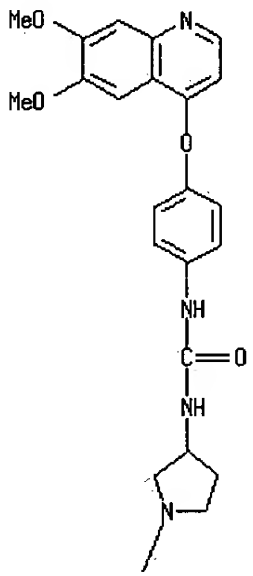


II

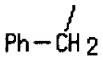
AB Title compds. [I; X = N, CH; R3, R4, R5, R6 independently = H, Cl, F, CH3, CH3O, NO2; A = 4-CH3C6H4CH2OCONH, 3-ClC6H4CH(CH3)OCONH, 4-FC6H4CH2OCONH, 2-ClC6H4CH(CH3)OCONH, 2-ClC6H4CH2CH2CH2OCONH, 4-CF3C6H4CH2OCONH,CH3(CH2)5OCONH, (CH3CH2)2N(CH2)3NHCSNH, YNHCONH, 4-ClC6H4O(CH2)2S, 4-ClC6H4(CH2)2NH, 3-BrC6H4CONHCSNH, C6H5COO, OH, OCH2COOCH3, OCH2COOH; Y = heterocycle, heterocyclylalkyl] and pharmaceutically acceptable salts are prepd. as remedies for diseases mediated by autophosphorylation of PDGF receptors, particularly useful as intimal thickening inhibitors. Thus, the title claimed compd. II was prepd. and biol. tested.

IT **347155-22-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of quinazolines and quinolines as remedies for diseases mediated by autophosphorylation of PDGF receptors)
RN 347155-22-0 HCAPLUS
CN Urea, N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-[1-(phenylmethyl)-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 20 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2000:628110 HCAPLUS
DOCUMENT NUMBER: 133:222450
TITLE: Preparation of arylsulfonylaminoalkynoates as metalloprotease inhibitors
INVENTOR(S): Natchus, Michael George; Bookland, Roger Gunnard; Almstead, Neil Gregory; Pikul, Stanislaw; De, Biswanath; Cheng, Menyan
PATENT ASSIGNEE(S): Procter & Gamble Co., USA
SOURCE: PCT Int. Appl., 120 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2000051975	A1	20000908	WO 2000-US5162	20000301	
W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
US 6197770	B1	20010306	US 2000-517080	20000301	
NZ 513831	A	20010928	NZ 2000-513831	20000301	
EP 1165501	A1	20020102	EP 2000-912064	20000301	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, IE, SI, LT, LV, FI, RO					
BR 2000008716	A	20020924	BR 2000-8716	20000301	
JP 2002538136	T2	20021112	JP 2000-602203	20000301	
AU 764051	B2	20030807	AU 2000-33860	20000301	
AU 2000033860	A5	20000921			
ZA 2001006967	A	20020313	ZA 2001-6967	20010823	
NO 2001004242	A	20010927	NO 2001-4242	20010831	
PRIORITY APPLN. INFO.:			US 1999-122644P	P	19990303
			WO 2000-US5162	W	20000301

OTHER SOURCE(S): MARPAT 133:222450

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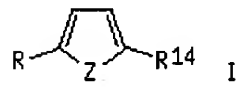


I

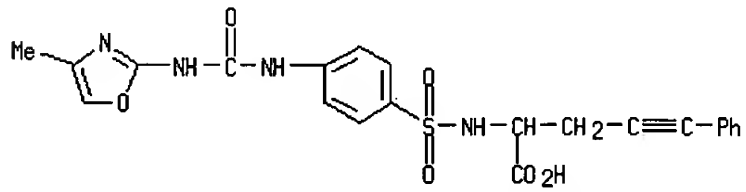
AB Title compds. [I; R = SO2NR2CR1(COX)CR3R4(CR5R5')kZ1R13; R1-R5,R5' = H or a substituent; R13 = H, (un)substituted alkyl, -CONH2, etc.; R14 = cycloalkyl, heterocyclyl, DZ2R27, (un)substituted NH2, etc.; D = O, S, CH:CH, N:N, etc.; R27 = alkyl, (hetero)aryl, etc.; X = OH or NHOH; Z = O, S, CH:CH, (alkyl)imino, etc.; Z1 = C≡C or (un)substituted CH:CH; Z2 = bond or (un)substituted alkylene] were prepd. as metalloprotease inhibitors (no data). Thus, PhC≡CCH2CH(NH2)CO2Me was N-acylated by 4-FC6H4C6H4(SO2Cl)-4 to give, after sapon., PhC≡CCH2(CO2H)NHSO2C6H4(C6H4F-4)-4.

IT **291533-73-8P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of arylsulfonylaminoalkynoates as metalloprotease inhibitors)

RN 291533-73-8 HCAPLUS

CN 4-Pentynoic acid, 2-[[[4-[[[(4-methyl-2-oxazolyl)amino]carbonyl]amino]phenyl]sulfonyl]amino]-5-phenyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 21 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:332965 HCAPLUS
DOCUMENT NUMBER: 131:44643
TITLE: Preparation of phenol derivatives as antioxidants and ACAT inhibitors
INVENTOR(S): Suzuki, Toshikazu; Ohmizu, Hiroshi; Hashimura, Yoshitada; Kubota, Hitoshi; Tanaka, Keiko
PATENT ASSIGNEE(S): Tanabe Seiyaku Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 70 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 11139969	A2	19990525	JP 1998-220951	19980805

PRIORITY APPLN. INFO.: JP 1997-212376 19970807
OTHER SOURCE(S): MARPAT 131:44643
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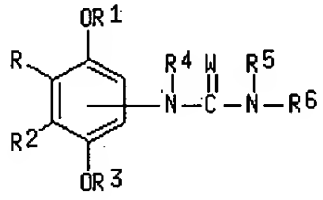

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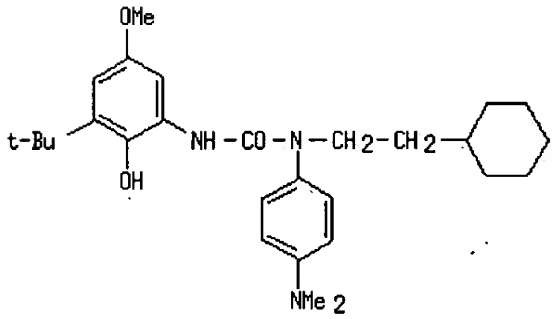
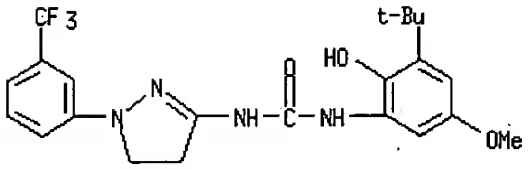


II

AB The title compds. I [R = H, (un)substituted alkyl, etc.; R1 = (un)substituted alkyl; R2 = (un)substituted alkyl, etc.; OR3= (protected) OH; R4 = H, (un)substituted alkyl, etc.; W = O, etc.; NR5R6 = (mono- or disubstituted) amino, etc.] are prepd. The title compd. II in vitro showed IC50 of 0.000067 μM against ACAT.

IT **195312-41-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of phenol derivs. as antioxidants and ACAT inhibitors)

RN 195312-41-5 HCAPLUS
CN Urea, N-[4,5-dihydro-1-[3-(trifluoromethyl)phenyl]-1H-pyrazol-3-yl]-N'-[3-(1,1-dimethylethyl)-2-hydroxy-5-methoxyphenyl]- (9CI) (CA INDEX NAME)



L24 ANSWER 22 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:325902 HCAPLUS
DOCUMENT NUMBER: 130:352546
TITLE: Preparation of amides containing leucine or methionine for inhibition of the interaction of vascular cell-adhesion molecule-1 (VCAM-1)and fibronectin with integrin very late antigen 4 (α4β1)
INVENTOR(S): Brittain, David Robert; Johnstone, Craig
PATENT ASSIGNEE(S): Zeneca Limited, UK
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9924398	A2	19990520	WO 1998-GB3334	19981109
WO 9924398	A3	19990805		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2308716	AA	19990520	CA 1998-2308716	19981109
AU 9910420	A1	19990531	AU 1999-10420	19981109
EP 1030835	A2	20000830	EP 1998-952872	19981109
EP 1030835	B1	20030122		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001522831	T2	20011120	JP 2000-520412	19981109
AT 231488	E	20030215	AT 1998-952872	19981109
ZA 9810330	A	19990512	ZA 1998-10330	19981111
NO 2000002158	A	20000711	NO 2000-2158	20000427
US 6344570	B1	20020205	US 2000-554224	20000711

PRIORITY APPLN. INFO.: GB 1997-23789 A 19971112
WO 1998-GB3334 W 19981109

OTHER SOURCE(S): MARPAT 130:352546
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

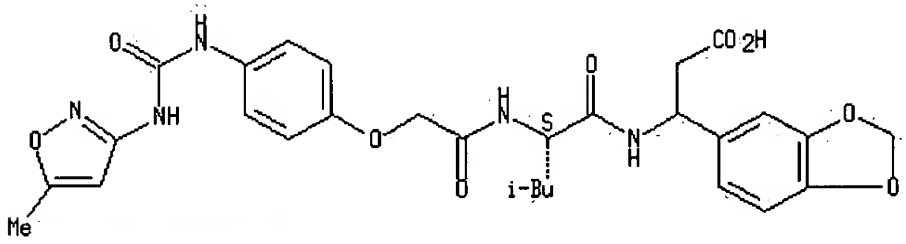
AB The title compds. [I; R1 = II (in the para or meta position); R2, R3 = H, NO2, alkyl, etc.; R2 and R3 together with the Ph to which they are attached form a 9-10 membered bicyclic ring system; R4 = alkyl; R5 = H, alkyl; R6 = alkyl, alkylcycloalkyl, alkylalkoxyl, etc.; R7 = alkyl, alkoxylcarbonyl, alkenyl, etc.; R8 = (un)substituted aryl, heteroaryl, bicyclic heteroaryl ring system linked to the nitrogen via a ring carbon, etc.; R9, R10 = H, alkyl; NR8R9 = dihydroindolyl, dihydroquinolinyl; R11 = CO2H, tetrazolyl, alkyl sulfonylcarbamyl, sulfo, sulfino; Y = O, S, SO2; m = 0-1; n = 0-4; with the proviso that when m and n cannot both be 0 and when m = 1, n = 0] and their pharmaceutically acceptable salts, useful in the treatment of multiple sclerosis, rheumatoid arthritis, asthma, coronary artery disease and psoriasis, were prepd. E.g., a multi-step synthesis of amide III was given. Compds. I are effective at 0.1-15 mg/kg/day.

IT 225101-10-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of amides contg. leucine or methionine for inhibition of the interaction of vascular cell-adhesion mol.-1 (VCAM-1)and fibronectin with integrin very late antigen 4 (α4β1))

RN 225101-10-0 HCAPLUS

CN β-Alanine, N-[[4-[[[(5-methyl-3-isoxazolyl)amino]carbonyl]amino]phenoxy]acetyl]-L-leucyl-3-(1,3-benzodioxol-5-yl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L24 ANSWER 23 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:311199 HCAPLUS
DOCUMENT NUMBER: 130:325145
TITLE: Preparation of aromatic heterocyclic compounds as antiinflammatory agents
INVENTOR(S): Regan, John R.; Cirillo, Pier F.; Hickey, Eugene R.; Moss, Neil; Cywin, Charles L.; Pargellis, Christopher; Gilmore, Thomas A.
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9923091	A1	19990514	WO 1998-US22907	19981029

W: AU, BG, BR, BY, CA, CN, CZ, HR, HU, ID, IL, JP, KR, KZ, LT, LV, MX, NO, NZ, PL, RO, RU, TR, UA, UZ, VN, YU
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

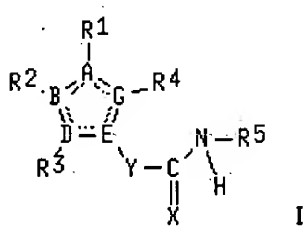
CA 2308428	AA	19990514	CA 1998-2308428	19981029	
AU 9913675	A1	19990524	AU 1999-13675	19981029	
US 6080763	A	20000627	US 1998-181743	19981029	
EP 1028953	A1	20000823	EP 1998-957405	19981029	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2001521934	T2	20011113	JP 2000-518962	19981029	
US 6228881	B1	20010508	US 1999-461446	19991214	
US 2001039290	A1	20011108	US 2001-808084	20010314	

PRIORITY APPLN. INFO.:

US 1997-64102P	P	19971103
US 1998-181743	A3	19981029
WO 1998-US22907	W	19981029
US 1999-461446	A3	19991214

OTHER SOURCE(S): MARPAT 130:325145

GI



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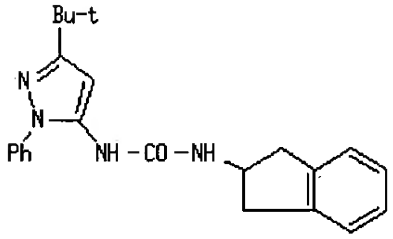


II

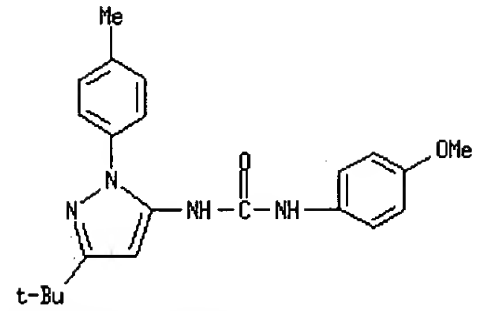
AB The title compds. I [A = C, N; B = C, N, O, etc.; D = C, N, S; E = C, N; G = C, S, N; X = S, O, etc.; Y = NH, etc.; R1 = (un)substituted, (partially or fully halogenated) alkyl, etc.; R2 is H, (partially or fully halogenated) alkyl, etc., when B is C or N; R3 is Ph, naphthyl, etc., when D is C or N; or R1R2 = fused Ph or pyridinyl ring; or R2R3 = fused Ph or pyridinyl ring; R4 is H, (partially or fully halogenated) alkyl when G is C or N; R5 is Ph, naphthyl, heteroaryl, etc.] are prepd. I inhibit prodn. of cytokines involved in immunoregulation and inflammation such as interleukin-1 and tumor necrosis factor. Pyrazole deriv. II was prepd. from phenylhydrazine and 4,4-dimethyl-3-oxopentanenitrile. Compds. of this invention had IC50 < 10 μM against TNF prodn. in an in vitro assay using THP cells.

IT **223724-76-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of arom. heterocyclic compds. as antiinflammatory agents)

RN 223724-76-3 HCAPLUS

CN Urea, N-[3-(1,1-dimethylethyl)-1-(4-methylphenyl)-1H-pyrazol-5-yl]-N'-(4-

methoxyphenyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 24 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

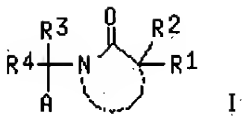
Full Text | Citing References

ACCESSION NUMBER: 1999:244635 HCAPLUS
DOCUMENT NUMBER: 130:296611
TITLE: Preparation of novel lactam as metalloprotease inhibitors
INVENTOR(S): Duan, Jinguw; Decicco, Carl P.; Wasserman, Zelda R.; Maduskuie, Thomas P., Jr.
PATENT ASSIGNEE(S): Du Pont Pharmaceuticals Company, USA
SOURCE: PCT Int. Appl., 333 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9918074	A1	19990415	WO 1998-US21037	19981002
W: AU, BR, CA, CN, CZ, EE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
ZA 9808967	A	20000403	ZA 1998-8967	19981001
CA 2305679	AA	19990415	CA 1998-2305679	19981002
AU 9896866	A1	19990427	AU 1998-96866	19981002
AU 747239	B2	20020509		
US 6057336	A	20000502	US 1998-165747	19981002
EP 1027332	A1	20000816	EP 1998-950954	19981002
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
BR 9815398	A	20001031	BR 1998-15398	19981002
EE 200000199	A	20010416	EE 2000-200000199	19981002
JP 2001519331	T2	20011023	JP 2000-514886	19981002
NO 2000000783	A	20000529	NO 2000-783	20000217

PRIORITY APPLN. INFO.: US 1997-62418P P 19971003
WO 1998-US21037 W 19981002

OTHER SOURCE(S): MARPAT 130:296611
GI



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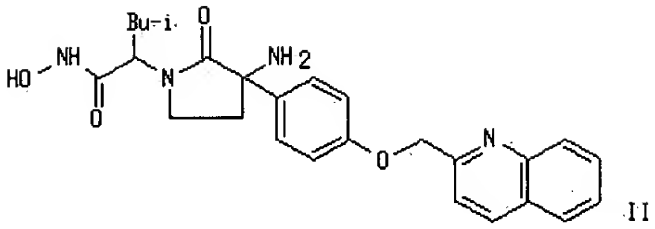


II

AB Title compds. [I; A is selected from COOH, CH2COOH, CONHOH, SH, CH2SH, PO(OH)2, etc.; ring B is a 4-8 membered cyclic amide contg. 0-3 heteroatoms from O, N, and S, etc.; R1 is phenylmethoxyphenyl, phenoxyphenyl, etc.; R2 is H, CH3, Et, i-Pr, etc.; R1-R2 combine to form heterocyclic; R3 is H, alkylene, heterocyclic, etc.; R4 is H, alkylene, etc.; R3-R4 combine to form heterocyclic], stereoisomer, and pharmaceutically acceptable salt thereof are prepd. as useful metalloprotease inhibitors. Thus, compd. II was prepd. via alkylation, oxidn., amination, and cyclization.

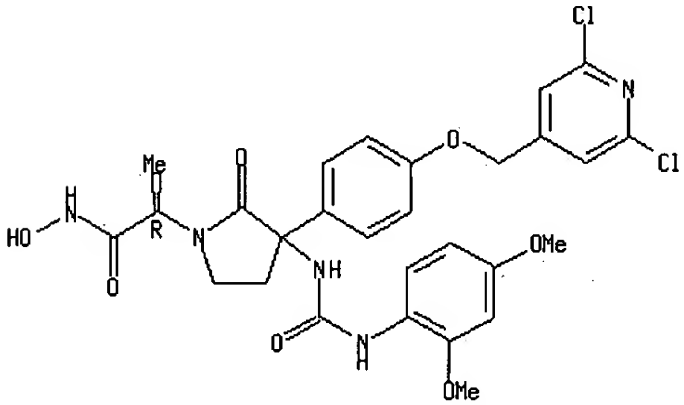
IT **223403-48-3P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of novel lactam metalloprotease inhibitors)

RN 223403-48-3 HCAPLUS

CN 1-Pyrrolidineacetamide, 3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-3-[[[(2,4-dimethoxyphenyl)amino]carbonyl]amino]-N-hydroxy-α-methyl-2-oxo-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 25 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

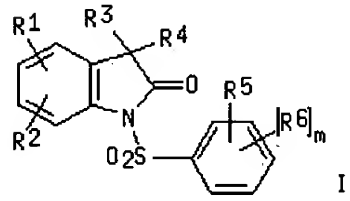
ACCESSION NUMBER: 1999:3288 HCAPLUS
DOCUMENT NUMBER: 130:66390
TITLE: Preparation of 1-benzenesulfonyl-1,3-dihydroindol-2-ones as vasopressin and/or oxytocin antagonists
INVENTOR(S): Di Malta, Alain; Foulon, Loic; Garcia, Georges; Nisato, Dino; Roux, Richard; Serradeil-Legal, Claudine; Valette, Gerard; Wagnon, Jean
PATENT ASSIGNEE(S): Sanofi, Fr.
SOURCE: U.S., 53 pp., Cont.-in-part of U.S. Ser. No. 129,310, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5849780	A	19981215	US 1994-323921	19941017
FR 2686878	A1	19930806	FR 1992-1034	19920130
FR 2686878	B1	19950630		
FR 2708605	A1	19950210	FR 1993-9404	19930730
EP 636608	A1	19950201	EP 1994-401737	19940728
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 5663431	A	19970902	US 1995-477571	19950607
US 5686624	A	19971111	US 1995-473302	19950607
US 5728723	A	19980317	US 1995-478738	19950607
US 5726322	A	19980310	US 1997-824305	19970326

PRIORITY APPLN. INFO.:

FR 1992-1034	A	19920130
FR 1993-9404	A	19930730
US 1993-129310	B2	19930930
EP 1994-401737	A	19940728
US 1994-323921	A3	19941017
US 1995-473302	A3	19950607

OTHER SOURCE(S): MARPAT 130:66390
GI



I

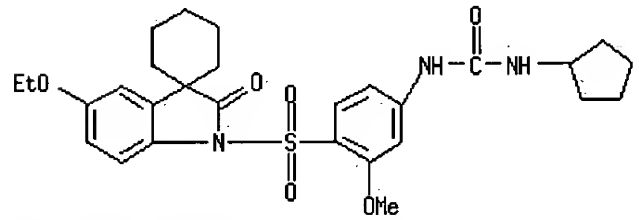
AB The title compds. [I; R1, R2 = H, OH, halo, etc.; R3R4 together with the carbon to which they are bonded = an optionally fused, (un)satd. (un)substituted C3-12 hydrocarbon ring; R5, R6 = H, halo, C1-7 alkyl, etc.; m = 1-4], having an affinity for the vasopressin V1 and V2 and/or oxytocin receptors, were prepd. Thus, treatment of 5-chloro-1,3-dihydro-3-spirocyclohexaneindol-2-one with NaH in THF followed by addn. of 2-methoxy-4-nitrobenzenesulfonyl chloride afforded I [R1 = 5-Cl; R2 = H; R3R4 = (CH2)5; R5 = 2-MeO; R6 = 4-NO2]. Biol. data for compds. I are given.

IT **161950-92-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); **THU (Therapeutic use)**;

THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of 1-benzenesulfonyl-1,3-dihydroindol-2-ones as vasopressin and/or oxytocin antagonists)

RN 161950-92-1 HCAPLUS

CN Spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one, 1'-[[4-[[(cyclopentylamino)carbonyl]amino]-2-methoxyphenyl]sulfonyl]-5'-ethoxy- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 26 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1998:42378 HCAPLUS
DOCUMENT NUMBER: 128:88682
TITLE: Preparation of hydroxyphenylureas as interleukin-8 receptor antagonists
INVENTOR(S): Widdowson, Katherine L.
PATENT ASSIGNEE(S): Smithkline Beecham Corp., USA; Widdowson, Katherine L.
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9749680	A1	19971231	WO 1997-US10903	19970624
W: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9734091	A1	19980114	AU 1997-34091	19970624
EP 912505	A1	19990506	EP 1997-930204	19970624
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI				
BR 9709952	A	19990810	BR 1997-9952	19970624
JP 2000514049	T2	20001024	JP 1998-503448	19970624
ZA 9705743	A	19971229	ZA 1997-5743	19970627
TW 408102	B	20001011	TW 1997-86109211	19970912
NO 9806110	A	19990223	NO 1998-6110	19981223
KR 2000022274	A	20000425	KR 1998-710694	19981226
US 6133319	A	20001017	US 1999-202569	19990819

PRIORITY APPLN. INFO.: US 1996-20658P P 19960627
US 1996-21973P P 19960627

WO 1997-US10903 W 19970624

OTHER SOURCE(S): MARPAT 128:88682

AB Title compds., e.g., RZNHC(:X)NHR1 [R = any functional moiety having an ionizable hydrogen and a pKa of ≤10 (sic); R1 = (un)substituted alk(en)yl or -alkynyl; Z = e.g., (un)substituted 1,2-phenylene] were prepd. Thus, 2-amino-5-nitrophenol was acylated by CH2:CHCH2NCO to give 2,4-(HO)(O2N)C6H3NHCONHCH2CH:CH2. Data for biol. activity of title compds. were given.

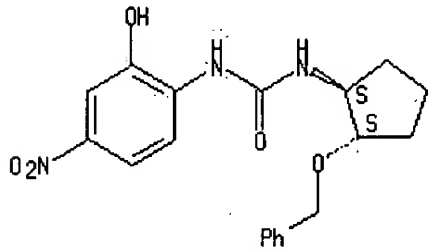
IT **201043-79-0P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of hydroxyphenylureas as interleukin-8 receptor antagonists)

RN 201043-79-0 HCAPLUS

CN Urea, N-(2-hydroxy-4-nitrophenyl)-N'-[2-(phenylmethoxy)cyclopentyl]-, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L24 ANSWER 27 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:589063 HCAPLUS

DOCUMENT NUMBER: 127:234183

TITLE: Ureidophenols as ACAT inhibitors and antioxidants

INVENTOR(S): Suzuki, Toshikazu; Ohmizu, Hiroshi; Hashimura, Yoshimasa; Kubota, Hitoshi; Tanaka, Keiko

PATENT ASSIGNEE(S): Tanabe Seiyaku Co., Ltd., Japan

SOURCE: Eur. Pat. Appl., 84 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 790240	A1	19970820	EP 1997-102315	19970213
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CA 2197364	AA	19970816	CA 1997-2197364	19970212
JP 10195037	A2	19980728	JP 1997-28582	19970213
US 5849732	A	19981215	US 1997-800680	19970214
CN 1165815	A	19971126	CN 1997-101973	19970217

PRIORITY APPLN. INFO.: JP 1996-28083 19960215
JP 1996-300032 19961112

OTHER SOURCE(S): MARPAT 127:234183

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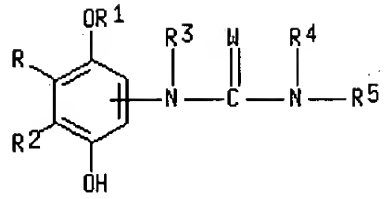
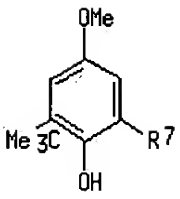


I



II

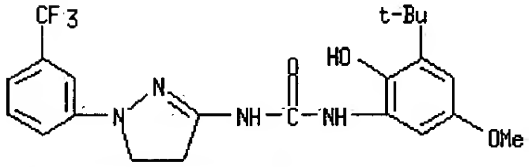
AB Ureidophenols I [R = H, alkyl, alkyloxy; R1 = alkyl; R2 = alkyl, alkoxy; R3 = H, alkyl, acyl; W = O, S or NR6; NR4R5 = (un)substituted NH2, N heterocycle; R6 = H, alkyl, aryl, OH, alkoxy] were prepd. I possess both an ACAT inhibitory activity and an antioxidative activity (no data). Thus, 4,2-MeO(Me3C)C6H3OH was treated with 4-MeOC6H4NH2 to give the azobenzene II [R7 = N:NC6H4OMe-4], which was O-protected, reduced to the amine, treated with PhNCO, and O-deprotected to give the ureidophenol II [R7 = NHCONHPh].

IT **195312-41-5P**

RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of ureidophenols as ACAT inhibitors and antioxidants)

RN 195312-41-5 HCAPLUS

CN Urea, N-[4,5-dihydro-1-[3-(trifluoromethyl)phenyl]-1H-pyrazol-3-yl]-N'-[3-□ (1,1-dimethylethyl)-2-hydroxy-5-methoxyphenyl]- (9CI) (CA INDEX NAME)



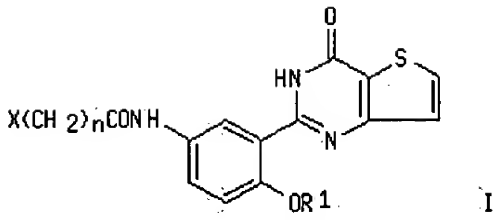
L24 ANSWER 28 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1996:241537 HCAPLUS
DOCUMENT NUMBER: 124:289561
TITLE: Preparation of thienopyrimidinones as cyclic GMP phosphodiesterase inhibitors
INVENTOR(S): Oota, Tomoki; Kawashima, Yutaka; Hatayama, Katsuo
PATENT ASSIGNEE(S): Taisho Pharma Co Ltd, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 20 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 07330777	A2	19951219	JP 1994-126555	19940608

PRIORITY APPLN. INFO.: JP 1994-126555 19940608
OTHER SOURCE(S): MARPAT 124:289561
GI



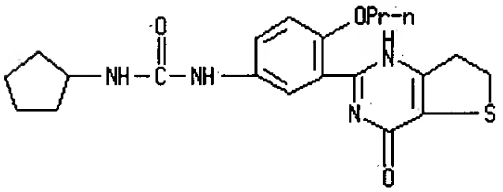
I

AB The title compds. I [R1 = alkyl; n = 0 or 1; X = halo, cycloalkyl, etc.] are prepd. I [X = morpholino; n = 0; R1 = ethyl] (prepn. given) at 28 μg/Kg decreased blood pressure in rats by 15 mmHg.

IT **175595-13-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of thienopyrimidinones as cyclic GMP phosphodiesterase inhibitors)

RN 175595-13-8 HCAPLUS

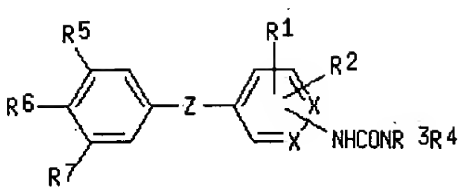
CN Urea, N-cyclopentyl-N'-[4-propoxy-3-(1,4,6,7-tetrahydro-4-oxothieno[3,2-d]pyrimidin-2-yl)phenyl]- (9CI) (CA INDEX NAME)



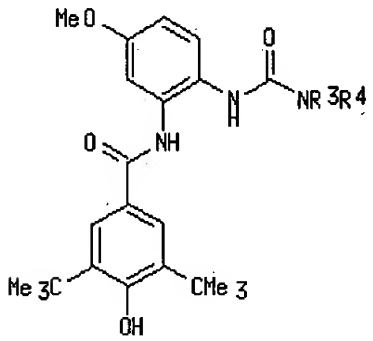
L24 ANSWER 29 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:890151 HCAPLUS
DOCUMENT NUMBER: 123:285554
TITLE: Preparation of arylureas as cholesterol acyltransferase inhibitors
INVENTOR(S): Sueda, Noriyoshi; Yamada, Kazuhiko; Yanai, Makoto; Miura, Katsutoshi; Horigome, Masato; Oshida, Norio; Hiramoto, Shigeru; Katsuyama, Koichi; Nakata, Fumihisa; et al.
PATENT ASSIGNEE(S): Nisshin Flour Milling Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 49 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 665216	A1	19950802	EP 1994-307398	19941010
EP 665216	B1	19971229		
R: DE, FR, GB, IT				
US 5576335	A	19961119	US 1994-314814	19940929
CA 2133394	AA	19950802	CA 1994-2133394	19940930
JP 07258199	A2	19951009	JP 1994-270205	19941011

PRIORITY APPLN. INFO.: JP 1994-27560 19940201
OTHER SOURCE(S): MARPAT 123:285554
GI



I



II

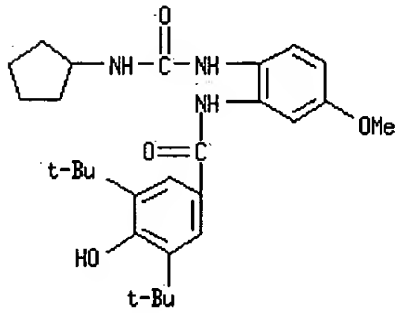
AB Title compds. [I; R1,R2 = H, halo, alkoxy; R3,R4 = H, (ar)alkyl, etc.; NR3R4 = heterocyclyl; R5,R7 = H, alkyl; R6 = OR8, N(R8)2; R6R7 = OCH2O, etc.; R8 = H, alkyl, CONHR3; X = N, CH; Z = CONR9, O2C, O(CH2)3, etc.; R9 = H, alkyl, alkanoyl, etc.] were prepd. Thus, 4-methoxy-2-nitroaniline was acylated by ClCO2Ph and the product amidated by cyclopentylamine to give, after hydrogenation and amidation by 3,5-di-tert-butyl-4-□ hydroxybenzoic acid, title compd. II (R3 = H, R4 = cyclopentyl). II (R3 = R4 = CH2Ph) gave 99% inhibition of cholesterol acyltransferase at 10-7M in vitro.

IT **169604-08-4P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of arylureas as cholesterol acyltransferase inhibitors)

RN 169604-08-4 HCAPLUS

CN Benzamide, N-[2-[[(cyclopentylamino)carbonyl]amino]-5-methoxyphenyl]-3,5-□ bis(1,1-dimethylethyl)-4-hydroxy- (9CI) (CA INDEX NAME)



L24 ANSWER 30 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1995:464454 HCAPLUS
DOCUMENT NUMBER: 122:213926
TITLE: 1-Benzenesulfonyl-1,3-dihydro-indol-2-one derivatives,

their preparation, and pharmaceutical compositions containing them.

INVENTOR(S): Di, Malta Alain; Foulon, Loic; Garcia, Georges; Nisato, Dino; Roux, Richard; Serradeil-Legal, Claudine; Valette, Gerard; Wagnon, Jean

PATENT ASSIGNEE(S): Sanofi, Fr.

SOURCE: Eur. Pat. Appl., 55 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

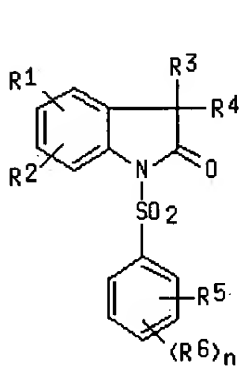
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 636608	A1	19950201	EP 1994-401737	19940728
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
FR 2708605	A1	19950210	FR 1993-9404	19930730
IL 110482	A1	19990411	IL 1994-110482	19940728
CA 2129215	AA	19950131	CA 1994-2129215	19940729
FI 9403570	A	19950131	FI 1994-3570	19940729
NO 9402834	A	19950131	NO 1994-2834	19940729
AU 9468789	A1	19950209	AU 1994-68789	19940729
AU 684791	B2	19980108		
ZA 9405656	A	19950309	ZA 1994-5656	19940729
HU 70408	A2	19951030	HU 1994-2232	19940729
RU 2141476	C1	19991120	RU 1994-27576	19940729
CN 1107467	A	19950830	CN 1994-114900	19940730
JP 07247269	A2	19950926	JP 1994-199069	19940801
US 5849780	A	19981215	US 1994-323921	19941017
US 5686624	A	19971111	US 1995-473302	19950607
US 5726322	A	19980310	US 1997-824305	19970326

PRIORITY APPLN. INFO.:

FR 1993-9404	A	19930730
FR 1992-1034	A	19920130
US 1993-129310	B2	19930930
EP 1994-401737	A	19940728
US 1994-323921	A3	19941017
US 1995-473302	A3	19950607

OTHER SOURCE(S): CASREACT 122:213926; MARPAT 122:213926

GI



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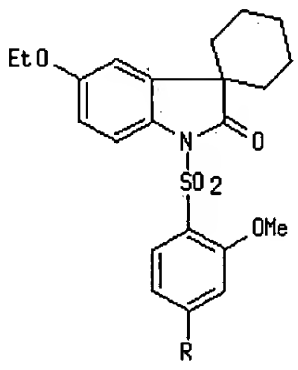


II

AB Title compds. I [R1, R2 = H, OH, halo, haloalkoxy, alkyl, CF3, alkoxy, etc.; R3, R4 = alkyl, cycloalkyl, Ph, PhCH2, hydroxyalkyl, etc.; or R3R4 = (CH2)pX(CH2)q; or R3R4 forms an (un)substituted (un)satd. hydrocarbon ring; R5, R6 = H, halo, alkyl, CF3, cyano, OH, NO2, (un)substituted NH2,

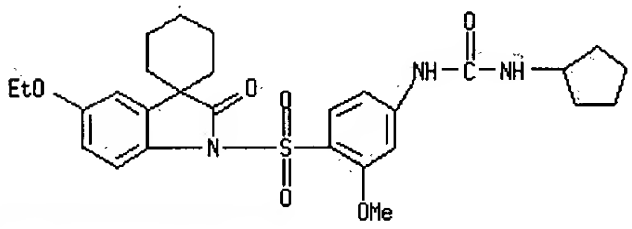
CO2H, etc.; X = O, SOn, NH or derivs.; m = 1, or (when R6 = halo, alkyl, or alkoxy) also 2-4, or (for multiple but different R6) also > 1; n = 0-2; (p + q) = 3-6; numerous addnl. definitions and provisos] and their salts are claimed. Over 80 synthetic examples are given. Thus, 5-ethoxy-1,3-dihydro-3-spirocyclohexaneindol-2-one [prepn. given] was treated with NaH in THF and then N-sulfonylated with 2-methoxy-4-nitrobenzenesulfonyl chloride. Redn. of the nitro group in the product with Fe and HCl and cyclization of the resultant amine with cis-1,4-dichloro-2-butene gave a mixt. of title compds. II [R = 1-pyrrolidinyl and 1-(3-pyrrolinyl)], which were hydrogenated over Pd/C to give II (R = 1-pyrrolidinyl). In various assays, I bound to V1 and V2 vasopressin receptors with IC50 values down to 10-7 and 10-9 M, resp., and bound to oxytocin receptors with IC50 down to 10-8 M. The compds. also showed oral activity (no data).

IT **161950-92-1P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of benzenesulfonyldihydroindolone derivs. as vasopressin and/or oxytocin antagonists)

RN 161950-92-1 HCAPLUS

CN Spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one, 1'-[[4-[[(cyclopentylamino)carbonyl]amino]-2-methoxyphenyl]sulfonyl]-5'-ethoxy- (9CI) (CA INDEX NAME)



L24 ANSWER 31 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

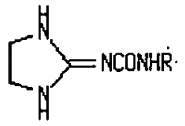
ACCESSION NUMBER: 1982:68993 HCAPLUS
DOCUMENT NUMBER: 96:68993
TITLE: N-(Substituted phenyl)-N'-(2-imidazolidinylidene)ureas
INVENTOR(S): Rasmussen, Chris R.
PATENT ASSIGNEE(S): McNeil Laboratories, Inc., USA
SOURCE: U.S., 7 pp. Cont.-in-part of U.S. 4,229,462.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4298746	A	19811103	US 1980-156900	19800606
US 4229462	A	19801021	US 1978-972579	19781222
ZA 7906965	A	19810729	ZA 1979-6965	19791221
GB 2113204	A1	19830803	GB 1982-21517	19820726
GB 2113204	B2	19840201		

PRIORITY APPLN. INFO.:

US 1978-972579	19781222
US 1978-972580	19781222
GB 1979-44114	19791221

OTHER SOURCE(S): CASREACT 96:68993
GI

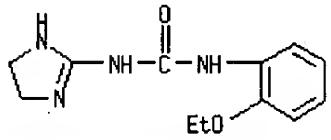


II

AB The reaction of 2-iminoimidazolidine (I) with RNCO (R = methyl-, chloro-, bromo-, or methoxyphenyl) yielded the resp. ureas II, which exhibited antihypertensive activity. I, 2,6-Cl2C6H3NCO, and Na2SO4 in THF-DMF was stirred overnight to give II (R = 2,6-Cl2C6H3).

IT **80625-17-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antihypertensive activity of)

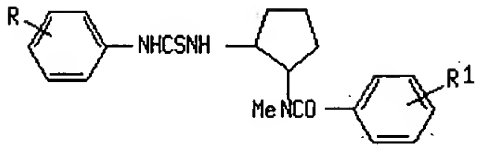
RN 80625-17-8 HCAPLUS
CN Urea, N-(4,5-dihydro-1H-imidazol-2-yl)-N'-(2-ethoxyphenyl)- (9CI) (CA INDEX NAME)



L24 ANSWER 32 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1981:132015 HCAPLUS
DOCUMENT NUMBER: 94:132015
TITLE: Interrelationship between anticonvulsant and enzyme inhibitor properties of N-methyl-N-[2-(1-arylthiocarbamido)]cyclopentyl]nitrobenzamides
AUTHOR(S): Pandey, Ghagwan R.; Singh, Shiva P.; Brumleve, Stanley J.; Parmar, Surendra S.
CORPORATE SOURCE: Dep. Pharmacol. Therapeutics, Lucknow Univ., Lucknow, 226003, India
SOURCE: Pharmacological Research Communications (1981), 13(1), 65-74
CODEN: PLRCAT; ISSN: 0031-6989
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB A series of N-methyl-N-[2-(1-arylthiocarbamido)cyclopentyl]nitrobenzamides I (R = H, 2-Me, 2-OMe etc; R' = 2- or 4-NO2) were synthesized and

evaluated for their anticonvulsant activity and potentiation of pentobarbital-induced hypnosis. These compds. were also investigated for their ability to inhibit pyruvate oxidase [9001-96-1] and monoamine oxidase [9001-66-5]. No structural correlation between the central nervous system depressant and the enzyme inhibitory properties of these I was apparent.

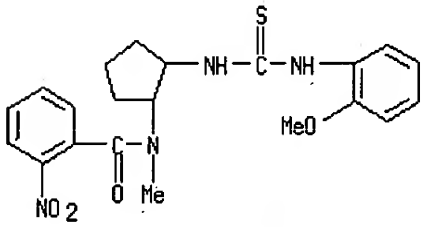
IT **77051-85-5P**

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

(prepn. and pharmacol. of, structure in relation to)

RN 77051-85-5 HCAPLUS

CN Benzamide, N-[2-[[[(2-methoxyphenyl)amino]thioxomethyl]amino]cyclopentyl]-N-methyl-2-nitro- (9CI) (CA INDEX NAME)



L24 ANSWER 33 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1971:141216 HCAPLUS
DOCUMENT NUMBER: 74:141216
TITLE: Chemotherapeutic agents against Mycobacterium tuberculosis. XXVI. Synthesis and antituberculous activity of phenylthiourea, p-ethoxyphenylthiourea, and 3-bromo-4-ethoxyphenylthiourea derivatives
AUTHOR(S): Fujikawa, Fukujiro; Hirai, Kunio; Hirayama, Teruhisa; Matsunashi, Teruki; Nakanishi, Yoshikuni; Kumoto, Kayoko; Shimizu, Tatsuzo; Sakaki, Chiichiro; Hamuro, Yoshitaro; et al.
CORPORATE SOURCE: Kyoto Coll. Pharm., Kyoto, Japan
SOURCE: Yakugaku Zasshi (1971), 91(2), 159-65
CODEN: YKKZAJ; ISSN: 0031-6903
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

GI For diagram(s), see printed CA Issue.

AB Seventy-five thioureas, comprising 27 derivs. of phenylthiourea (I), 25 of p-ethoxyphenylthiourea (II), and 23 of 3-bromo-4-ethoxyphenylthiourea (III), were prepd. from corresponding phenyl isothiocyanates and tested for antibacterial activity against a strain of human-type, drug-sensitive Mycobacterium tuberculosis in vitro. Six of them were active, but their min. inhibitory concns. (MIC) were significantly higher than those of control agents, such as isoniazid and p-aminosalicylic acid. The MIC of 1-phenyl-3-[4-(dimethylamino)-phenyl]-2-thiourea and 1-(4-ethoxyphenyl)-3-(4-bromophenyl)-2-thiourea were 3.13 and 6.25 °mg/ml, resp.

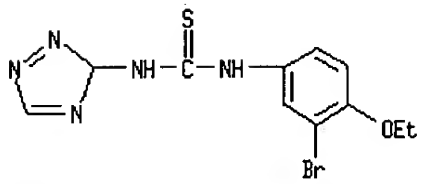
IT **31864-67-2**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(antitubercular activity of)

RN 31864-67-2 HCAPLUS

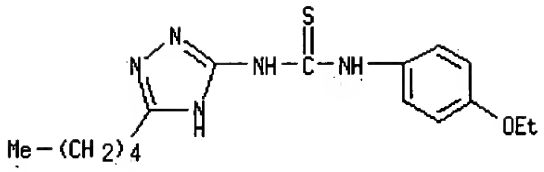
CN Urea, 1-(3-bromo-4-ethoxyphenyl)-2-thio-3-s-triazol-3-yl- (8CI) (CA INDEX NAME)



L24 ANSWER 34 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1969:103962 HCAPLUS
DOCUMENT NUMBER: 70:103962
TITLE: Synthesis and study of thiocarbamide derivatives. IV. Correlation between structure and tuberculostatic activity of 1H-1,2,4-triazole, 1,3-indandione, and 4-methoxybenzaldehyde thiourea derivatives
AUTHOR(S): Grinsteins, V.; Medne, K.; Sausins, A.; Cipens, G.; Bokalders, R.
CORPORATE SOURCE: Inst. Org. Sin., Riga, USSR
SOURCE: Latvijas PSR Zinatnu Akademijas Vestis, Kimijas Serija (1968), (6), 691-8
CODEN: LZAKAM; ISSN: 0002-3248
DOCUMENT TYPE: Journal
LANGUAGE: Russian
GI For diagram(s), see printed CA Issue.
AB The tuberculostatic activity of some thioureas was detd. in vitro, using the drug-sensitive Mycobacterium tuberculosis strains H37Rv and Ravenel and also the resistant strains Vallee and D. The following I were tested (R and R' given): Ph, H; Me, H; H, OEt (II); Me, OEt (III); Pr, OEt (IV); Me(CH2)4, OEt (V); Me, OPr (VI); Me, O(CH2)4Me (VII). VIII and 5-thiocarbamoyl-1H-1,2,4-triazole were similarly tested. Only IIVII had high antitubercular activity. The following IX were also tested (R and R' given): H, H; H, OMe; H, o-OMe; H, OEt (X); H, Me; H, Br; H, I; OMe, H; OMe, OMe; OMe, o-OMe; OMe, OEt; OMe, Me; OMe, I; OMe, Br. IX had low antitubercular activity, except X. The following XI were also tested (R given): Ph; p-MeC6H4 (XII); p-EtOC6H4; p-Pr-OC6H4; p-iso-PrOC6H4; p-BuOC6H4; p-iso-BuOC6H4; p-Me-(CH2)4OC6H4; p-BrC6H4; p-IC6H4; 2-C10H7. Also tested was the ortho analog (XIII) of XII. XII and XIII had some activity. XIV (R = MeO, Br, or I) were practically inactive. p-[2,5-MeO(HCO)C6H3NHCSNH]C6H4R (R = H, MeO, o-EtO, PrO, BuO, Me(CH2)4O, or Br) and 4,3-MeO(p-BuOC6H4NHCSNH)-C6H3CH:NNHC(NH2):NH.HCl were studied. In this class also, alkoxy-contg. compds. were most active. Addn. of blood serum to the nutrient medium of the microorganisms reduced the activity of the most effective compds. to 1/30-1/2.
IT 21731-95-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(tuberculostatic activity of)
RN 21731-95-3 HCAPLUS
CN Urea, 1-(p-ethoxyphenyl)-3-(5-pentyl-s-triazol-3-yl)-2-thio- (8CI) (CA INDEX NAME)



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     (FILE 'HOME' ENTERED AT 21:09:03 ON 29 MAR 2004)

     FILE 'REGISTRY' ENTERED AT 21:09:18 ON 29 MAR 2004
L1              STRUCTURE UPLOADED
L2            2 S L1
L3          787 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 21:10:37 ON 29 MAR 2004
L4           46 S L3/THU
L5            5 S L4 AND DUMAS, J?/AU
L6           41 S L4 NOT L5
L7            0 S L6 AND KHIRE, U?/AU
L8            1 S L6 AND LOWINGER, T?/AU
L9            1 S L6 AND PAULSEN, H?/AU
L10          40 S L6 NOT L8
L11           1 S L10 AND PAULSEN, H?/AU
L12          39 S L10 NOT L11
L13           0 S L12 AND RIEDL, B?/AU
L14           0 S L12 AND SCOTT, W?/AU
L15           0 S L12 AND SMITH, R?/AU
L16           0 S L12 AND WOOD, W?/AU
L17           0 S L12 AND HATOUM-MOKDAD, H?/AU
L18           0 S L12 AND JOHNSON, J?/AU
L19           0 S L12 AND LEE, W?/AU
L20           0 S L12 AND REDMAN, A?/AU
L21           0 S L12 AND SIBLEY, R?/AU
L22           0 S L12 AND RENICK, J?/AU
L23           5 S L12 AND  CANC?
L24          34 S L12 NOT L23
L25           0 S L24, IBIB ABS FHITSTR, 1-34

=> s l3
L26         151 L3

=> file caold
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   244.75     400.80

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                   -31.88     -31.88

FILE 'CAOLD' ENTERED AT 21:16:57 ON 29 MAR 2004
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FILE COVERS 1907-1966
FILE LAST UPDATED:  01 May 1997 (19970501/UP)
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  This file contains CAS Registry Numbers for easy and accurate
  substance identification.  Title keywords, authors, patent
  assignees, and patent information, e.g., patent numbers, are
  now searchable from 1907-1966.  TIFF images of CA abstracts
  printed between 1907-1966 are available in the PAGE
  display formats.

  This file supports REGlstRY for direct browsing and searching of
  all substance data from the REGISTRY file.  Enter HELP FIRST for
  more information.

=> d his

     (FILE 'HOME' ENTERED AT 21:09:03 ON 29 MAR 2004)

     FILE 'REGISTRY' ENTERED AT 21:09:18 ON 29 MAR 2004
L1              STRUCTURE UPLOADED
L2            2 S L1
L3          787 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 21:10:37 ON 29 MAR 2004
L4           46 S L3/THU
L5            5 S L4 AND DUMAS, J?/AU
L6           41 S L4 NOT L5
L7            0 S L6 AND KHIRE, U?/AU
L8            1 S L6 AND LOWINGER, T?/AU
L9            1 S L6 AND PAULSEN, H?/AU
L10          40 S L6 NOT L8
L11           1 S L10 AND PAULSEN, H?/AU
L12          39 S L10 NOT L11
L13           0 S L12 AND RIEDL, B?/AU
L14           0 S L12 AND SCOTT, W?/AU
L15           0 S L12 AND SMITH, R?/AU
L16           0 S L12 AND WOOD, W?/AU
L17           0 S L12 AND HATOUM-MOKDAD, H?/AU
L18           0 S L12 AND JOHNSON, J?/AU
L19           0 S L12 AND LEE, W?/AU
L20           0 S L12 AND REDMAN, A?/AU
L21           0 S L12 AND SIBLEY, R?/AU
L22           0 S L12 AND RENICK, J?/AU
L23           5 S L12 AND  CANC?
L24          34 S L12 NOT L23
L25           0 S L24, IBIB ABS FHITSTR, 1-34
L26         151 S L3

     FILE 'CAOLD' ENTERED AT 21:16:57 ON 29 MAR 2004

=> s 13
L27          14 L3

=> s 13 and can?
             14 L3
          17544 CAN?
L28           0 L3 AND CAN?

=> d 127, all, 1-14

L27  ANSWER 1 OF 14  CAOLD  COPYRIGHT 2004 ACS on STN
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Full Text

AN CA65:720g CAOLD
TI 5-methyloxazoline, urea derivs. of
PA Chemische Werke Albert
DT Patent
TI urea derivs. of 5-methyloxazoline
AU Zimmermann, Rolf; Koch, K.; Englisch, A.
DT Patent

	PATENT NO.	KIND	DATE
PI	GB 1023386		

IT 1750-38-5 1750-39-6 **1963-13-9** 2318-76-5 6449-68-9 31788-64-4

L27 ANSWER 2 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full Text

AN CA65:204b CAOLD
TI color couplers
AU Franchi, Luigi; Magagnoli, R.
DT Patent

	PATENT NO.	KIND	DATE
PI	FR 1403481		

IT 2489-28-3 10555-22-3 10555-23-4 13014-99-8 **30424-07-8**

L27 ANSWER 3 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full Text

AN CA64:16037g CAOLD
TI 1-fluoroalkyl-2-pyrazolin-5-one color couplers
PA Gevaert-Agfa N. V.
DT Patent

	PATENT NO.	KIND	DATE
PI	NL 6509593		
	BE 667370		
	FR 1441166		

IT 1439-40-3 1439-63-0 1439-64-1 1908-58-3 5355-07-7 5355-08-8
5376-72-7 5376-74-9 5376-75-0 5376-76-1 5376-77-2 5376-78-3
5376-79-4 5376-80-7 5377-19-5 5528-93-8 5529-15-7 5529-17-9
5529-18-0 **5529-19-1** 5529-20-4 5529-21-5 5529-22-6 5529-23-7
5529-24-8 5529-25-9 5529-26-0 5529-27-1 6887-07-6 96764-55-5

L27 ANSWER 4 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full Text

AN CA64:9862b CAOLD
TI mercaptan-forming couplers
AU Barr, Charles R.; Williams, J.; Whitmore, K. E.
PA Eastman Kodak Co.
DT Patent

	PATENT NO.	KIND	DATE
PI	US 3227554		1966

IT 5083-12-5 5083-13-6 5083-14-7 5083-15-8 5083-16-9 5083-17-0
5083-18-1 5083-19-2 5083-20-5 5083-21-6 5083-22-7 5083-23-8
5083-24-9 5104-70-1 5104-71-2 5104-72-3 5104-73-4 5104-74-5
5104-75-6 5104-76-7 5104-77-8 5104-78-9 5104-79-0 5104-80-3
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5563-00-8 5563-01-9 5577-21-9 5577-22-0 5577-23-1 5577-24-2
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106438-97-5 106439-05-8 108015-55-0 108015-56-1

L27 ANSWER 5 OF 14 CAOLD COPYRIGHT 2004 ACS on STN
AN CA64:5237c CAOLD
TI magenta photographic couplers
AU Bellone, Domenico; Chittolini, U.; Guzzi, A.
DT Patent
IT 614-16-4 1779-08-4 1788-10-9 2412-05-7 4581-46-8 4622-67-7
4640-64-6 4644-43-3 4644-44-4 4644-45-5 4644-46-6 4644-47-7
4644-48-8 4644-49-9 4644-50-2 4644-51-3 4644-52-4 4644-53-5
4644-54-6 4644-55-7 4644-56-8 4644-57-9 4644-58-0 4644-59-1
4681-06-5 4692-10-8 **4772-97-8** 4779-36-6 4779-37-7

L27 ANSWER 6 OF 14 CAOLD COPYRIGHT 2004 ACS on STN
Full Text
AN CA64:3550f CAOLD
TI cyclohept[d]imidazoles
AU Sunagawa, Genshun; Nakao, H.
PA Sankyo Co., Ltd.
DT Patent

PATENT NO.	KIND	DATE
JP 65020707		1965

IT **2048-43-3** 2048-44-4 2048-45-5 2048-46-6 2048-47-7 2048-48-8
2048-49-9 2132-29-8 2132-30-1 2409-67-8 2535-45-7 2536-06-3
2536-07-4

L27 ANSWER 7 OF 14 CAOLD COPYRIGHT 2004 ACS on STN
Full Text
AN CA63:1790e CAOLD
TI 5-methyloxazolidine derivs.
PA Chemische Werke Albert
DT Patent

PATENT NO.	KIND	DATE
BE 643289		
FR M3206		

IT 1750-37-4 1750-38-5 **1963-13-9** 1969-12-6 2318-76-5 31788-64-4

L27 ANSWER 8 OF 14 CAOLD COPYRIGHT 2004 ACS on STN
AN CA63:713h CAOLD
TI dry spinning of acetate fibers - (I) viscosity of the spinning solns.
AU Kamiya, Takuro; Hirokawa, K.
TI processing synthetic fibers
AU Usenko, V. A.
IT 1533-33-1 1533-35-3 1695-96-1 **1702-39-2**

L27 ANSWER 9 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full Text

AN CA62:16256d CAOLD
TI pyrazolopyrroles
AU Grandberg, I. I.
DT Patent

PATENT NO.	KIND	DATE
SU 168299		
BE 654108		
FR 1415852		

IT 1058-48-6 1059-72-9 1107-42-2 1107-43-3 1107-45-5 1590-67-6
1590-68-7 1590-73-4 1632-33-3 1806-69-5 1806-71-9 1806-72-0
1806-73-1 1837-70-3 2046-36-8 2046-37-9 2046-39-1 2046-40-4
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2048-43-3 2048-44-4 2048-45-5 2048-46-6 2048-57-9 2048-99-9
2049-00-5 2049-01-6 2144-96-9 2144-97-0 2144-99-2 2145-00-8
2145-01-9 2145-02-0 2235-84-9 2235-85-0 2311-90-2 2409-67-8
2536-06-3 3141-57-9 3141-94-4 3141-95-5 3486-41-7 95445-05-9

L27 ANSWER 10 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full Text

AN CA62:1249g CAOLD
TI color correction in color photography
AU Magagnoli, Remo; Bellone, D.
PA Ferrania Societa per Azioni
DT Patent

PATENT NO.	KIND	DATE
DE 1168769		

IT 1533-32-0 1533-33-1 **1702-39-2** 2489-00-1

L27 ANSWER 11 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full Text

AN CA62:681a CAOLD
TI couplers for photographic emulsion color development
AU Bellone, Domenico; Magagnoli, R.
PA Ferrania Societa per Azioni
DT Patent

PATENT NO.	KIND	DATE
DE 1150577		

IT 402-36-8 2489-27-2 2489-28-3 2489-29-4 **2489-30-7** 2489-31-8
2489-54-5 2489-55-6 2489-56-7 2489-57-8 2489-58-9 2673-00-9
2702-96-7

L27 ANSWER 12 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full Text

AN CA60:702a CAOLD
TI heat-developable diazotype materials
AU Schaeffer, Andre
PA Etablissements Bauchet & Cie
DT Patent

PATENT NO.	KIND	DATE
FR 1325692		

GB 1041022
IT 15006-70-9 58725-40-9 90230-09-4 94298-72-3 94489-23-3 95168-57-3
98564-39-7 100197-36-2 101174-68-9 103104-27-4 106041-87-6 106198-30-5
106951-55-7 **107012-82-8** **107541-74-2** 107926-51-2

L27 ANSWER 13 OF 14 CAOLD COPYRIGHT 2004 ACS on STN
Full Text
AN CA60:701h CAOLD
TI color couplers
PA Ferrania Societa per Azioni
DT Patent
TI purple, photographic color coupler
AU Bellone, Domenico; Magagnoli, R.
DT Patent

PATENT NO.	KIND	DATE
DE 1147483		

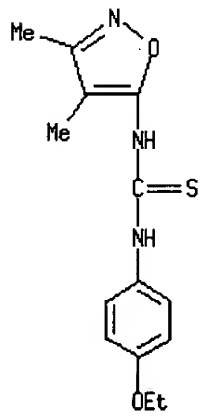
IT 6752-38-1 **92873-76-2**

L27 ANSWER 14 OF 14 CAOLD COPYRIGHT 2004 ACS on STN
AN CA53:6122i CAOLD
TI synthesis of asym. substituted derivs. of thiourea with potential tuberculostatic activity
AU Oeriu, Simion; Voinescu, M.; Wexler, B.; Gloter, E.
IT 1138-72-3 1142-30-9 100615-38-1 **100720-16-9** 100875-53-4 100875-54-5
101264-75-9 101872-56-4

=> **fil reg; d acc 100720-16-9; fil CAOLD**

FILE 'REGISTRY' ENTERED AT 21:18:21 ON 29 MAR 2004

ANSWER 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 100720-16-9 REGISTRY
CN Urea, 1-(3,4-dimethyl-5-isoxazolyl)-3-(p-ethoxyphenyl)-2-thio- (6CI) (CA INDEX NAME)
FS 3D CONCORD
MF C14 H17 N3 O2 S
SR CAOLD
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

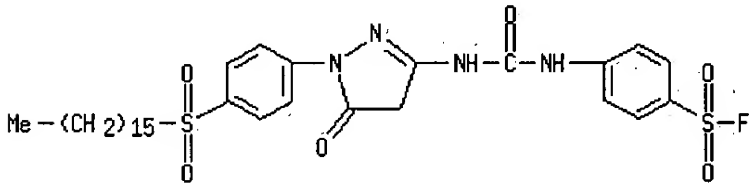
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

FILE 'CAOLD' ENTERED AT 21:18:42 ON 29 MAR 2004

=> fil reg; d acc 2048-43-3; fil CAOLD

FILE 'REGISTRY' ENTERED AT 21:19:20 ON 29 MAR 2004

ANSWER 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 2048-43-3 REGISTRY
CN Sulfanilyl fluoride, N-[[1-[p-(hexadecylsulfonyl)phenyl]-5-oxo-2-pyrazolin-3-yl]carbamoyl]- (7CI, 8CI) (CA INDEX NAME)
FS 3D CONCORD
MF C32 H45 F N4 O6 S2
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

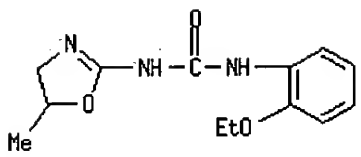
2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

FILE 'CAOLD' ENTERED AT 21:19:21 ON 29 MAR 2004

=> fil reg; d acc 1963-13-9; fil CAOLD

FILE 'REGISTRY' ENTERED AT 21:19:46 ON 29 MAR 2004

ANSWER 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 1963-13-9 REGISTRY
CN Urea, 1-(o-ethoxyphenyl)-3-(5-methyl-2-oxazolin-2-yl)- (7CI, 8CI) (CA INDEX NAME)
FS 3D CONCORD
MF C13 H17 N3 O3
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS
(*File contains numerically searchable property data)



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2 REFERENCES IN FILE CAPLUS (1907 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

FILE 'CAOLD' ENTERED AT 21:19:46 ON 29 MAR 2004

=> **fil reg; d acc 1963-13-9; fil CAOLD**

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.68	421.14

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-31.88

FILE 'REGISTRY' ENTERED AT 21:22:27 ON 29 MAR 2004
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 28 MAR 2004 HIGHEST RN 668418-93-7
DICTIONARY FILE UPDATES: 28 MAR 2004 HIGHEST RN 668418-93-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

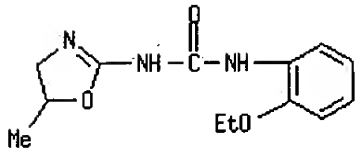
Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

ANSWER 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 1963-13-9 REGISTRY
CN Urea, 1-(o-ethoxyphenyl)-3-(5-methyl-2-oxazolin-2-yl)- (7CI, 8CI) (CA
INDEX NAME)
FS 3D CONCORD
MF C13 H17 N3 O3
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS

(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

FILE 'CAOLD' ENTERED AT 21:22:27 ON 29 MAR 2004

=> **log y**

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FULL ESTIMATED COST	0.42	423.75

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-31.88

STN INTERNATIONAL LOGOFF AT 21:22:39 ON 29 MAR 2004

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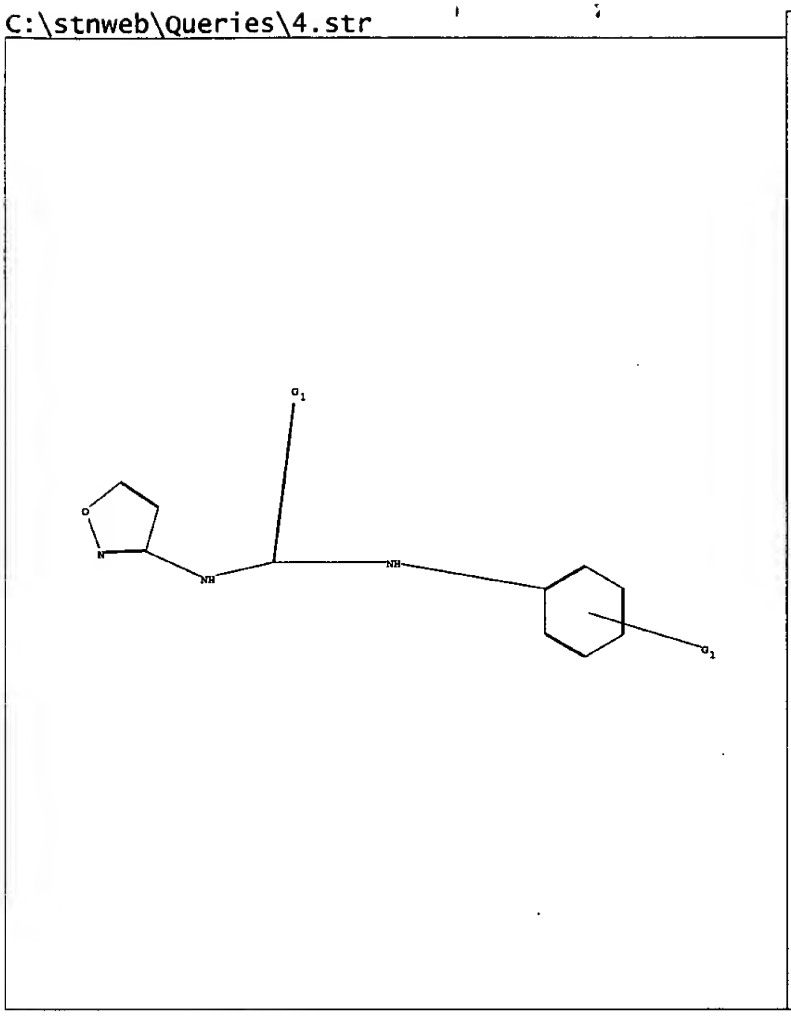

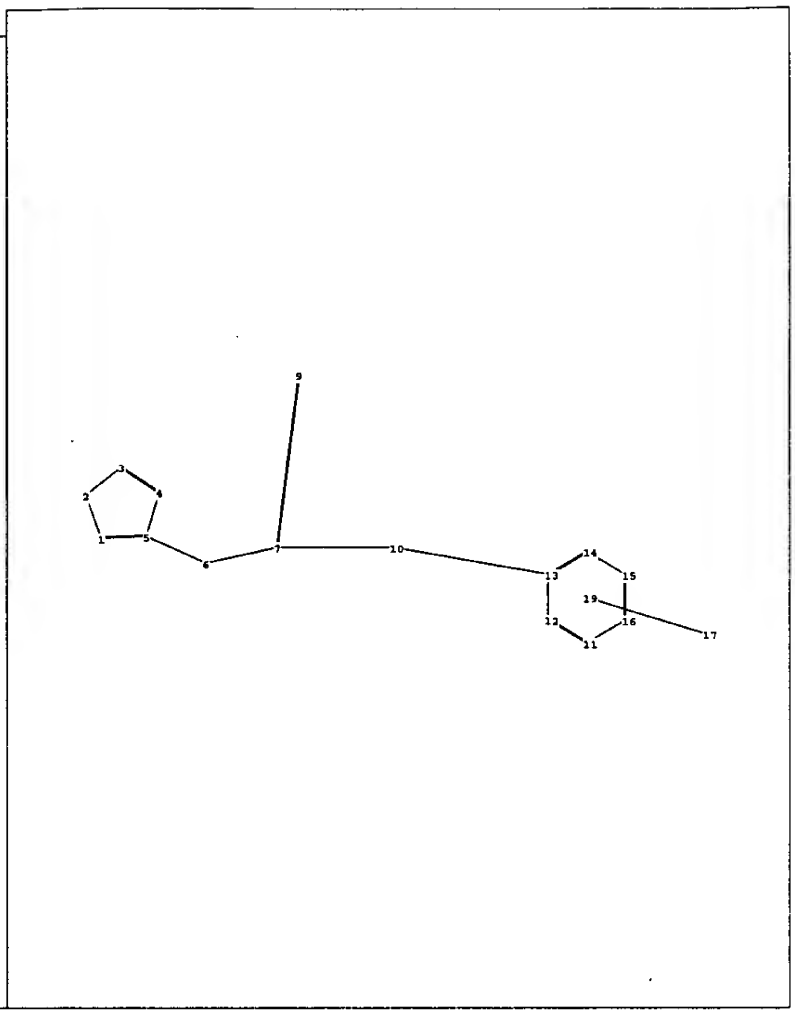

chain nodes :
6 7 9 10 17
ring nodes :
1 2 3 4 5 11 12 13 14 15 16
chain bonds :
5-6 6-7 7-9 7-10 10-13
ring bonds :
1-2 1-5 2-3 3-4 4-5 11-12 11-16 12-13 13-14 14-15 15-16
exact/norm bonds :
1-5 5-6 6-7 7-9 7-10 10-13
exact bonds :
1-2 2-3 3-4 4-5
normalized bonds :
11-12 11-16 12-13 13-14 14-15 15-16
isolated ring systems :
containing 1 :

G1:O,S

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 9:CLASS 10:CLASS 11:Atom
12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:CLASS 19:CLASS

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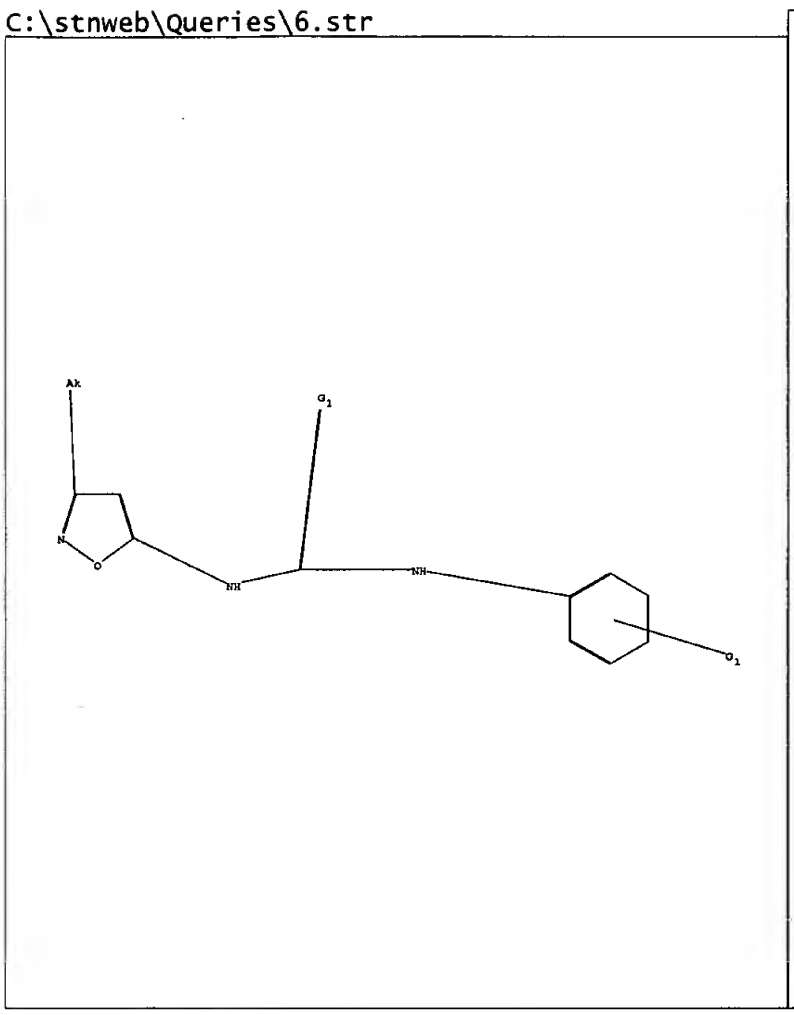

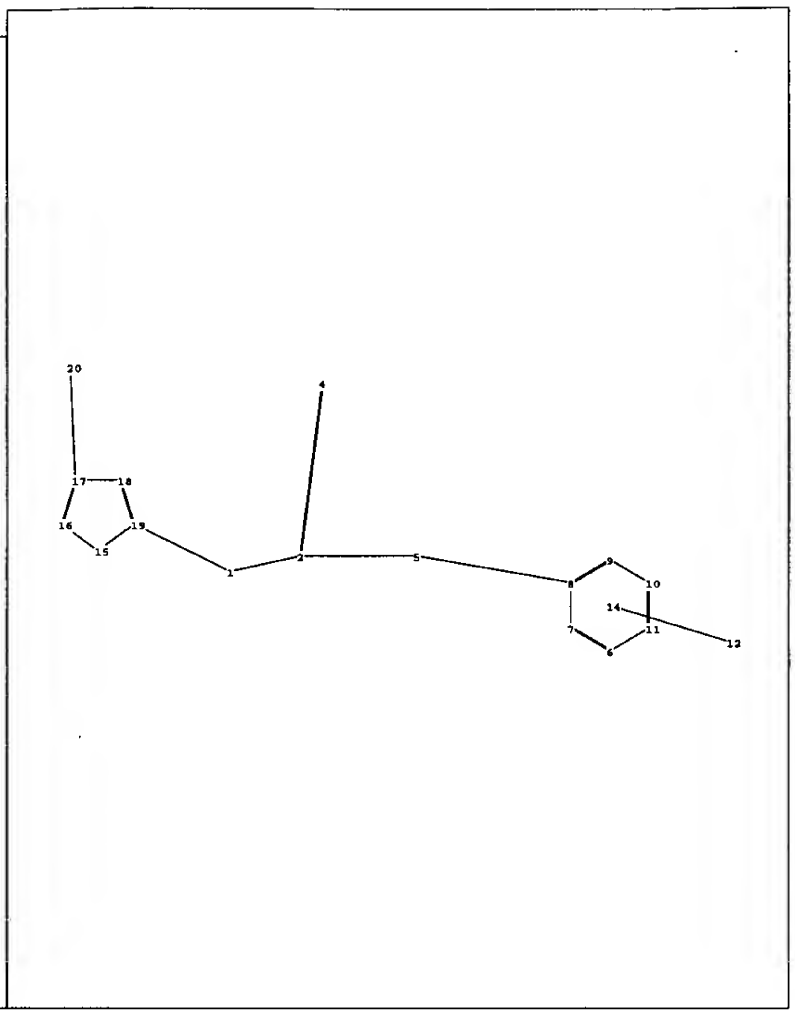

chain nodes :
1 2 4 5 12 20
ring nodes :
6 7 8 9 10 11 15 16 17 18 19
chain bonds :
1-2 1-19 2-4 2-5 5-8 17-20
ring bonds :
6-7 6-11 7-8 8-9 9-10 10-11 15-16 15-19 16-17 17-18 18-19
exact/norm bonds :
1-2 1-19 2-4 2-5 5-8 16-17 17-20
exact bonds :
15-16 15-19 17-18 18-19
normalized bonds :
6-7 6-11 7-8 8-9 9-10 10-11
isolated ring systems :
containing 6 : 15 :

G1:O,S

Match level :
1:CLASS 2:CLASS 4:CLASS 5:CLASS 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:CLASS 14:CLASS 15:Atom 16:Atom 17:Atom 18:Atom 19:CLASS 20:CLASS

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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1            Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2            "Ask CAS" for self-help around the clock
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                    present
 NEWS  4   DEC 08   INPADOC: Legal Status data reloaded
 NEWS  5   SEP 29   DISSABS now available on STN
 NEWS  6   OCT 10   PCTFULL: Two new display fields added
 NEWS  7   OCT 21   BIOSIS file reloaded and enhanced
 NEWS  8   OCT 28   BIOSIS file segment of TOXCENTER reloaded and enhanced
 NEWS  9   NOV 24   MSDS-CCOHS file reloaded
 NEWS 10   DEC 08   CABA reloaded with left truncation
 NEWS 11   DEC 08   IMS file names changed
 NEWS 12   DEC 09   Experimental property data collected by CAS now available
                    in REGISTRY
 NEWS 13   DEC 09   STN Entry Date available for display in REGISTRY and CA/CAplus
 NEWS 14   DEC 17   DGENE: Two new display fields added
 NEWS 15   DEC 18   BIOTECHNO no longer updated
 NEWS 16   DEC 19   CROPU no longer updated; subscriber discount no longer
                    available
 NEWS 17   DEC 22   Additional INPI reactions and pre-1907 documents added to CAS
                    databases
 NEWS 18   DEC 22   IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
 NEWS 19   DEC 22   ABI-INFORM now available on STN
 NEWS 20   JAN 27   Source of Registration (SR) information in REGISTRY updated
                    and searchable
 NEWS 21   JAN 27   A new search aid, the Company Name Thesaurus, available in
                    CA/CAplus
 NEWS 22   FEB 05   German (DE) application and patent publication number format
                    changes
 NEWS 23   MAR 03   MEDLINE and LMEDLINE reloaded
 NEWS 24   MAR 03   MEDLINE file segment of TOXCENTER reloaded
 NEWS 25   MAR 03   FRANCEPAT now available on STN
 NEWS 26   MAR 29   Pharmaceutical Substances (PS) now available on STN
 NEWS 27   MAR 29   WPIFV now available on STN
 NEWS 28   MAR 29   No connect hour charges in WPIFV until May 1, 2004
 NEWS 29   MAR 29   New monthly current-awareness alert (SDI) frequency in RAPRA

 NEWS EXPRESS  MARCH 5 CURRENT WINDOWS VERSION IS V7.00A, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 3 MARCH 2004
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

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  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 23:30:16 ON 29 MAR 2004
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=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 23:30:21 ON 29 MAR 2004
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Property values tagged with IC are from the ZIC/VINITI data file
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STRUCTURE FILE UPDATES:   28 MAR 2004  HIGHEST RN 668418-93-7
DICTIONARY FILE UPDATES:  28 MAR 2004  HIGHEST RN 668418-93-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
L1      STRUCTURE UPLOADED

=>  l1
L1 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d l1
L1 HAS NO ANSWERS
L1              STR
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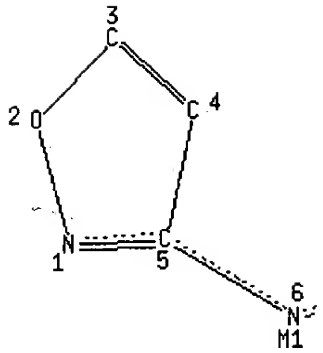
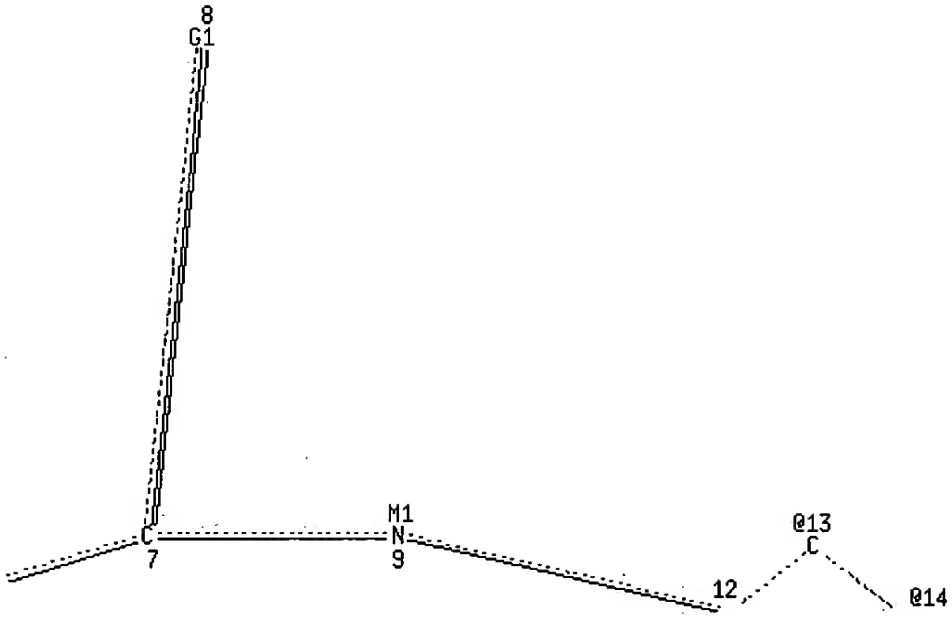
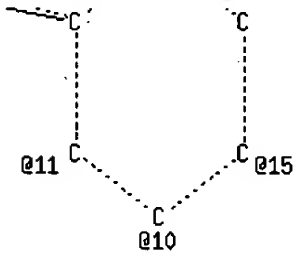
O 17 S 18



Page 1-A



Page 1-B



Page 2-B

G1 @16

Page 2-C

VAR G1=17/18

VPA 16-10/11/13/14/15 S

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NODE ATTRIBUTES:
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HCOUNT   IS M1      AT   9
NSPEC    IS R       AT   1
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NSPEC    IS C       AT  16
DEFAULT MLEVEL IS ATOM
MLEVEL   IS CLASS   AT   6  7  9 17 18
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC   5
NUMBER OF NODES IS  18

STEREO ATTRIBUTES: NONE


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SAMPLE SCREEN SEARCH COMPLETED -     50 TO ITERATE

100.0% PROCESSED      50 ITERATIONS                              15 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          576 TO     1424
PROJECTED ANSWERS:              68 TO      532

L2            15 SEA SSS SAM L1

=> s l1 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 23:32:31 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    845 TO ITERATE

100.0% PROCESSED     845 ITERATIONS                             238 ANSWERS
SEARCH TIME: 00.00.01

L3           238 SEA SSS FUL L1

=> file hcaplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   156.68     156.89
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FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004
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FILE COVERS 1907 - 29 Mar 2004 VOL 140 ISS 14
FILE LAST UPDATED: 28 Mar 2004 (20040328/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s l3
L4 11 L3

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665 DUMAS, J?/AU
L5 2 L4 AND DUMAS, J?/AU

=> **d l5, ibib abs fhitstr, 1-2**

L5 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:425745 HCAPLUS
DOCUMENT NUMBER: 131:87909
TITLE: Inhibition of p38 kinase activity using substituted heterocyclic ureas
INVENTOR(S): **Dumas, Jacques**; Khire, Uday; Lowinger, Timothy Bruno; Paulsen, Holger; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Lee, Wendy; Redman, Aniko
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932111	A1	19990701	WO 1998-US26080	19981222

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,

FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2315720	AA	19990701	CA 1998-2315720	19981222
AU 9919971	A1	19990712	AU 1999-19971	19981222
AU 739642	B2	20011018		
EP 1041982	A1	20001011	EP 1998-964709	19981222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001526223	T2	20011218	JP 2000-525102	19981222

PRIORITY APPLN. INFO.: US 1997-995750 A 19971222
WO 1998-US26080 W 19981222

OTHER SOURCE(S): MARPAT 131:87909

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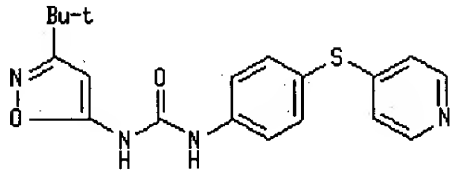
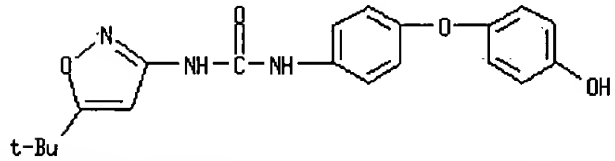


II

AB A method for treatment of p38-mediated disease other than cancer comprises administration of ANHCONHB [I; A = substituted isoxazolyl, pyrazolyl, thienyl, furyl; B = (substituted) mono-, di-, or tricyclic aryl, heteroaryl contg. ≥1 5-6 membered arom. structure contg. 0-4 N, O, or S atoms]. Reaction of 4-(4-pyridinylthio)aniline with 3-tert-butyl-5-isoxazolyl isocyanate in toluene gave title compd. II. In an in vitro p38 kinase assay, I displayed IC50 values of 1-10 μM.

IT **228999-08-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of substituted heterocyclic ureas for treatment of p38 kinase-mediated diseases other than cancer)

RN 228999-08-4 HCAPLUS
CN Urea, N-[5-(1,1-dimethylethyl)-3-isoxazolyl]-N'-[4-(4-hydroxyphenoxy)phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:425740 HCAPLUS
DOCUMENT NUMBER: 131:73648
TITLE: Inhibition of raf kinase using substituted heterocyclic ureas
INVENTOR(S): **Dumas, Jacques**; Khire, Uday; Lowinger, Timothy Bruno; Paulsen, Holger; Riedl, Bernd; Scott, William

J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Lee, Wendy; Redman, Aniko

PATENT ASSIGNEE(S): Bayer Corporation, USA

SOURCE: PCT Int. Appl., 163 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932106	A1	19990701	WO 1998-US26078	19981222
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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2315717	AA	19990701	CA 1998-2315717	19981222
AU 9921989	A1	19990712	AU 1999-21989	19981222
EP 1047418	A1	20001102	EP 1998-965981	19981222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001526220	T2	20011218	JP 2000-525097	19981222
BR 9814374	A	20020514	BR 1998-14374	19981222
NO 2000003232	A	20000821	NO 2000-3232	20000621
BG 104597	A	20010228	BG 2000-104597	20000712

PRIORITY APPLN. INFO.: US 1997-996343 A 19971222
WO 1998-US26078 W 19981222

OTHER SOURCE(S): MARPAT 131:73648

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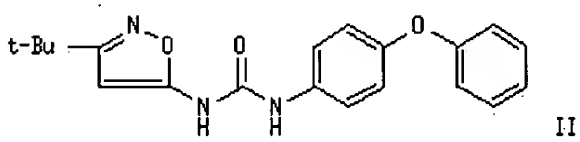


II

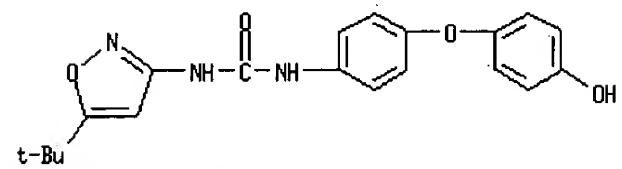
AB A method for treatment of cancerous cell growth mediated by raf kinase comprises administration of urea derivs. ANHCONHB [I; A = substituted isoxazolyl, thienyl, thiadiazolyl, furyl, pyrazolyl, etc.; B = (substituted) mono-, di-, or tricyclic aryl, heteroaryl contg. ≥1 5-6 membered arom. structure contg. 0-4 N, O, or S atoms]. Reaction of 4-phenyloxyphenyl isocyanate with 5-amino-3-tert-butylisoxazole in methylene chloride and heating at reflux temp. for 2 days gave title compd. II. In an in vitro raf kinase assay, I displayed IC50 values of 1-10 μM.

IT **228999-08-4P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(prepn. of substituted heterocyclic ureas for treatment of cancerous cell growth mediated by raf kinase)

RN 228999-08-4 HCAPLUS
CN Urea, N-[5-(1,1-dimethylethyl)-3-isoxazolyl]-N'-[4-(4-hydroxyphenoxy)phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 23:30:16 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 23:30:21 ON 29 MAR 2004
L1 STRUCTURE UPLOADED
L2 15 S L1
L3 238 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004
L4 11 S L3
L5 2 S L4 AND DUMAS, J?/AU

=> s l4 not l5
L6 9 L4 NOT L5

=> d l6 and khire, u?/au
'U?' MUST END IN '/Q', '/A', '/L', '/S' OR '/B'
The saved name for a query (or structure or screen set) must end with '/Q'. The saved name for an answer set must end with '/A'. The saved name for an L# list must end with '/L'. SDI request names must end with '/S'. To see a list of all saved query, answer set,, and L# list names for this loginid, enter "DISPLAY SAVED" at an arrow prompt (=>). Enter "DISPLAY SAVED/S" to see a list of SDI request names. Enter "DISPLAY SAVED/B" to see a list of BATCH search requests.

=> s l6 and khire, u?/au
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L7 0 L6 AND KHIRE, U?/AU

=> s l6 and lowinger, t?/au
41 LOWINGER, T?/AU
L8 1 L6 AND LOWINGER, T?/AU

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L8 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:746592 HCAPLUS
DOCUMENT NUMBER: 136:95577
TITLE: Discovery of heterocyclic ureas as a new class of raf kinase inhibitors: identification of a second generation lead by a combinatorial chemistry approach

AUTHOR(S): Smith, R. A.; Barbosa, J.; Blum, C. L.; Bobko, M. A.; Caringal, Y. V.; Dally, R.; Johnson, J. S.; Katz, M. E.; Kennure, N.; Kingery-Wood, J.; Lee, W.; **Lowinger, T. B.**; Lyons, J.; Marsh, V.; Rogers, D. H.; Swartz, S.; Walling, T.; Wild, H.

CORPORATE SOURCE: Department of Chemistry Research, Bayer Research Center, West Haven, CT, 06516, USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (2001), 11(20), 2775-2778
CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

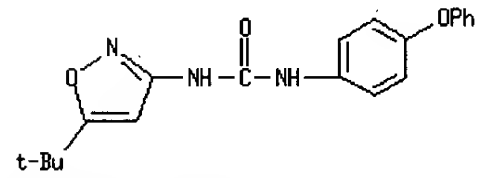
LANGUAGE: English

AB Heterocyclic ureas, such as N-3-thienyl N'-aryl ureas, have been identified as novel inhibitors of raf kinase, a key mediator in the ras signal transduction pathway. Structure-activity relationships were established, and the potency of the screening hit was improved 10-fold to IC50=1.7 μM. A combinatorial synthesis approach enabled the identification of a breakthrough lead (IC50=0.54 μM) for a second generation series of heterocyclic urea raf kinase inhibitors.

IT **228998-90-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(heterocyclic ureas as raf kinase inhibitors)

RN 228998-90-1 HCAPLUS

CN Urea, N-[5-(1,1-dimethylethyl)-3-isoxazolyl]-N'-(4-phenoxyphenyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L2          15 S L1
L3         238 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004
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L5           2 S L4 AND DUMAS, J?/AU
L6           9 S L4 NOT L5
L7           0 S L6 AND KHIRE, U?/AU
L8           1 S L6 AND LOWINGER, T?/AU

=> s l6 not l8
L9           8 L6 NOT L8
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           660 PAULSEN, H?/AU
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            30 REDMAN, A?/AU
L18          0 L9 AND REDMAN, A?/AU

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L20          0 L9 AND RENICK, J?/AU

=> d his

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L1               STRUCTURE UPLOADED
L2           15 S L1
L3          238 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004
L4           11 S L3
L5            2 S L4 AND DUMAS, J?/AU
L6            9 S L4 NOT L5
L7            0 S L6 AND KHIRE, U?/AU
L8            1 S L6 AND LOWINGER, T?/AU
L9            8 S L6 NOT L8
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L17             0 S L9 AND LEE, W?/AU
L18             0 S L9 AND REDMAN, A?/AU
L19             0 S L9 AND SIBLEY, R?/AU
L20             0 S L9 AND RENICK, J?/AU

=> d 19, ibib abs fhistr, 1-8
'FHISTR' IS NOT A VALID FORMAT FOR FILE 'HCAPLUS'

The following are valid formats:

ABS --------- GI and AB
ALL --------- BIB, AB, IND, RE
APPS -------- AI, PRAI
BIB --------- AN, plus Bibliographic Data and PI table (default)
CAN --------- List of CA abstract numbers without answer numbers
CBIB -------- AN, plus Compressed Bibliographic Data
DALL -------- ALL, delimited (end of each field identified)
DMAX -------- MAX, delimited for post-processing
FAM --------- AN, PI and PRAI in table, plus Patent Family data
FBIB -------- AN, BIB, plus Patent FAM
IND --------- Indexing data
IPC --------- International Patent Classifications
MAX --------- ALL, plus Patent FAM, RE
PATS -------- PI, SO
SAM --------- CC, SX, TI, ST, IT
SCAN -------- CC, SX, TI, ST, IT (random display, no answer numbers;
              SCAN must be entered on the same line as the DISPLAY,
              e.g., D SCAN or DISPLAY SCAN)
STD --------- BIB, IPC, and NCL

IABS -------- ABS, indented with text labels
IALL -------- ALL, indented with text labels
IBIB -------- BIB, indented with text labels
IMAX -------- MAX, indented with text labels
ISTD -------- STD, indented with text labels

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

HIT --------- Fields containing hit terms
HITIND ------ IC, ICA, ICI, NCL, CC and index field (ST and IT)
              containing hit terms
HITRN ------- HIT RN and its text modification
HITSTR ------ HIT RN, its text modification, its CA index name, and
              its structure diagram
HITSEQ ------ HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and
              its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its
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              structure diagram, plus NTE and SEQ fields
KWIC -------- Hit term plus 20 words on either side
OCC --------- Number of occurrence of hit term and field in which it occurs

To display a particular field or fields, enter the display field
codes.  For a list of the display field codes, enter HELP DFIELDS at
an arrow prompt (=>).  Examples of formats include: TI; TI,AU; BIB,ST;
TI,IND; TI,SO.  You may specify the format fields in any order and the
information will be displayed in the same order as the format
specification.

All of the formats (except for SAM, SCAN, HIT, HITIND, HITRN, HITSTR,
FHITSTR, HITSEQ, FHITSEQ, KWIC, and OCC) may be used with DISPLAY ACC
to view a specified Accession Number.
ENTER DISPLAY FORMAT (BIB):end

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     (FILE 'HOME' ENTERED AT 23:30:16 ON 29 MAR 2004)

     FILE 'REGISTRY' ENTERED AT 23:30:21 ON 29 MAR 2004
L1              STRUCTURE UPLOADED
L2           15 S L1
L3          238 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004
L4           11 S L3
L5            2 S L4 AND DUMAS, J?/AU
L6            9 S L4 NOT L5
L7            0 S L6 AND KHIRE, U?/AU
L8            1 S L6 AND LOWINGER, T?/AU
L9            8 S L6 NOT L8
L10           0 S L9 AND PAULSEN, H?/AU
L11           0 S L9 AND RIEDL, B?/AU
L12           0 S L9 AND SCOTT, W?/AU
L13           0 S L9 AND SMITH, R?/AU
L14           0 S L9 AND WOOD, J?/AU
L15           0 S L9 AND HATOUM-MOKDAD, H?/AU
L16           0 S L9 AND JOHNSON, W?/AU
L17           0 S L9 AND LEE, W?/AU
L18           0 S L9 AND REDMAN, A?/AU
L19           0 S L9 AND SIBLEY, R?/AU
L20           0 S L9 AND RENICK, J?/AU

=> d 19, ibib abs fhitstr, 1-8

L9   ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

NO

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ACCESSION NUMBER:         2004:182368  HCAPLUS
TITLE:                    Three hybrid assay system for isolating ligand-binding
                          polypeptides and for isolating small mol. ligands
INVENTOR(S):              Come, Jon H.; Becker, Frank; Kley, Nikolai A.;
                          Reichel, Christoph
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 238 pp., Cont.-in-part of U.S.
                          Ser. No. 91,177.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
```

FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004043388	A1	20040304	US 2002-234985	20020903
US 2003165873	A1	20030904	US 2002-91177	20020304

PRIORITY APPLN. INFO.:
US 2001-272932P P 20010302
US 2001-278233P P 20010323
US 2001-329437P P 20011015
US 2002-91177 A2 20020304

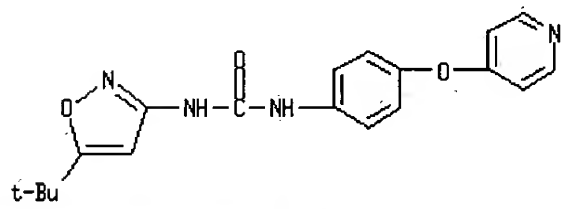
AB The invention provides compns. and methods for isolating ligand-binding polypeptides for a user-specified ligand, and for isolating small mol. ligands for a user-specified target polypeptide using an improved class of hybrid ligand compds. Prepn. of compds., e.g a methotrexate moiety linked by a polyethylene gycol moiety to dexamethasone, is described.

IT INDEXING IN PROGRESS

IT 228999-48-2D, conjugates
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands)

RN 228999-48-2 HCAPLUS

CN Urea, N-[5-(1,1-dimethylethyl)-3-isoxazolyl]-N'-[4-(4-pyridinyloxy)phenyl]- (9CI) (CA INDEX NAME)



L9 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

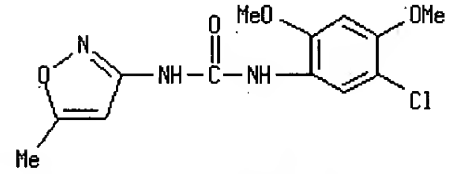
ACCESSION NUMBER: 2003:892762 HCAPLUS
DOCUMENT NUMBER: 139:395938
TITLE: Preparation of ureas as positive allosteric modulators of the nicotinic acetylcholine receptor
INVENTOR(S): Piotrowski, David W.; Rogers, Bruce N.; McWhorter, William W., Jr.; Walker, Daniel P.; Corbett, Jeffrey W.; Groppi, Vincent E., Jr.; Rudmann, Daniel G.
PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA
SOURCE: PCT Int. Appl., 159 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003093250	A2	20031113	WO 2003-US11493	20030428

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD,
RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG

US 2003236287 A1 20031225 US 2003-423062 20030425
PRIORITY APPLN. INFO.: US 2002-377364P P 20020503
US 2003-456941P P 20030324
OTHER SOURCE(S): MARPAT 139:395938
AB ANHCXNHB [X = O, S; A = (un)substituted Ph, 6-membered N heteroaryl; B = (un)substituted 5-6-membered heteroaryl] were prepd. to treat diseases or conditions in which the α7 nAChR is known to be involved (no data). Thus, 2,4-Me(MeO)C6H3NH2 was treated with 3-F3CC6H4CNO to give 2,4-Me(MeO)C6H3NHCONHC6H4CF3-3.
IT 501925-31-1P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of ureas as pos. allosteric modulators of the nicotinic acetylcholine receptor)
RN 501925-31-1 HCAPLUS
CN Urea, N-(5-chloro-2,4-dimethoxyphenyl)-N'-(5-methyl-3-isoxazolyl)- (9CI) (CA INDEX NAME)



L9 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

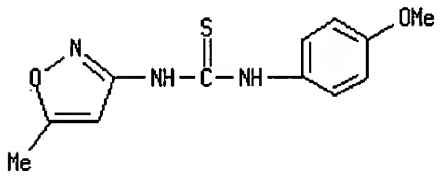
Full Text | Citing References

ACCESSION NUMBER: 2003:571600 HCAPLUS
DOCUMENT NUMBER: 140:59591
TITLE: Synthesis and biological activity of 3-aryl-1-(5-methyl-4-acetyl-3-isoxazolyl)-2-thioxo-(1H,3H,5H)-pyrimidine-4,6-diones
AUTHOR(S): Swamy, S. Narasimha; Murthy, A. Krishna; Rajanarendar, E.
CORPORATE SOURCE: Department of Chemistry, Kakatiya University, Warangal, 506 009, India
SOURCE: Indian Journal of Heterocyclic Chemistry (2003), 12(4), 357-360
CODEN: IJCHEI; ISSN: 0971-1627
PUBLISHER: Prof. R. S. Varma
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 3-Aryl-1-(5-methyl-4-acetyl-3-isoxazolyl)-2-thioxo-(1H,3H,5H)-pyrimidine-4,6-diones were prepd. by the interaction of 3-aryl-1-(5-methyl-3-isoxazolyl)thioureas with malonic acid in acetyl chloride. The 3-isoxazolylthiourea compds. were made by the reaction of 3-amino-5-methylisoxazole with aryl-isothiocyanates. Antibacterial and antifungal activity of 3-isoxazolylthiourea and 3-isoxazolyl-2-thioxo-(1H,3H,5H)-pyrimidine-4,6-diones compds. were studied.
IT 638164-94-0P

RL: BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(antibacterial and antifungal activities; prepn. and biol. activity of 3-aryl-1-(5-methyl-3-isoxazolyl)thioureas and 3-aryl-1-(5-methyl-4-acetyl-3-isoxazolyl)-2-thioxo-(1H,3H,5H)-pyrimidine-4,6-diones)

RN 638164-94-0 HCAPLUS

CN Thiourea, N-(4-methoxyphenyl)-N'-(5-methyl-3-isoxazolyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

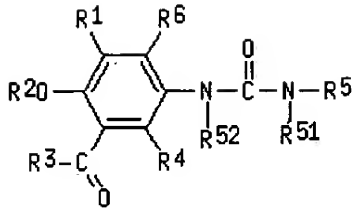
ACCESSION NUMBER: 2003:282524 HCAPLUS
DOCUMENT NUMBER: 138:304064
TITLE: Preparation of phenylurea derivatives as vanilloid receptor agonists
INVENTOR(S): Matsumoto, Takahiro; Yamamoto, Masataka; Nagabukuro, Hiroshi; Mochizuki, Manabu
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 293 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003029199	A1	20030410	WO 2002-JP9995	20020927
WO 2003029199	C2	20030925		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2001-300564 A 20010928
OTHER SOURCE(S): MARPAT 138:304064
GI



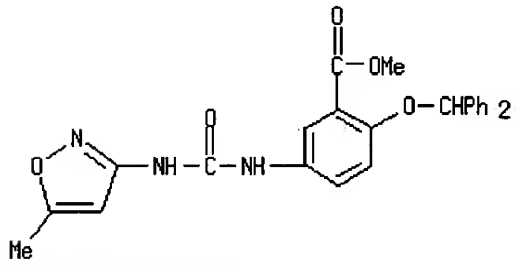
I

AB The title compds. I [R1, R4 and R6 are each independently hydrogen, halogeno, or hydrocarbyl; R2 is hydrocarbyl or a heterocyclic group; R3 is hydrocarbyl, etc.; R5 is hydrocarbyl or a heterocyclic group (except quinolyl) and R51 is hydrogen or hydrocarbyl, or R5 and R51 together with the nitrogen atom adjacent thereto may form a ring; and R52 is hydrogen or hydrocarbyl] are prepd. I are useful for the treatment of pain, urinary incontinence, etc. In a tail flick test using mice, one compd. of this invention showed a min. ED of 1 mg/kg.

IT 508214-80-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of phenylurea derivs. as vanilloid receptor agonists)

RN 508214-80-0 HCAPLUS

CN Benzoic acid, 2-(diphenylmethoxy)-5-[[[(5-methyl-3-isoxazolyl)amino]carbonyl]amino]-, methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:849617 HCAPLUS
DOCUMENT NUMBER: 137:370101
TITLE: Preparation of quinoline derivatives having azolyl group and quinazoline derivatives as antitumor agents
INVENTOR(S): Kubo, Kazuo; Sakai, Teruyuki; Nagao, Rika; Fujiwara, Yasunari; Isoe, Toshiyuki; Hasegawa, Kazumasa
PATENT ASSIGNEE(S): Kirin Beer Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002088110	A1	20021107	WO 2002-JP4279	20020426

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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

JP 2003012668	A2	20030115	JP 2002-126869	20020426
US 2003087907	A1	20030508	US 2002-132473	20020426
EP 1382604	A1	20040121	EP 2002-724651	20020426

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

NO 2003004595	A	20031219	NO 2003-4595	20031014

PRIORITY APPLN. INFO.: JP 2001-132775 A 20010427
WO 2002-JP4279 W 20020426

OTHER SOURCE(S): MARPAT 137:370101

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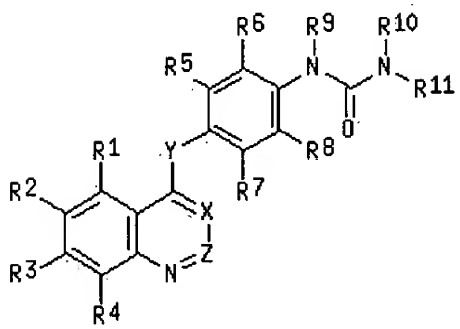


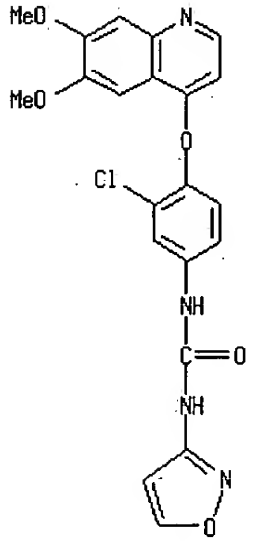
I

AB N-[(4-quinolinyl or 4-quinazolinyl)thio or -oxy]phenyl-N'-azolylurea derivs. represented by the formula (I) or pharmaceutically acceptable salts or solvates thereof [wherein X, Z = CH, N; Y = O, S; R1, R2, R3 = H, NO2, NH2, each (un)substituted C1-6 alkyl or alkoxy or C2-6 alkenyl or alkynyl; R4 = H; R5-R8 = H, halo, C1-4 alkyl, alkoxy, or alkylthio, CF3, NO2, NH2; R9, R10 = C1-6 alkyl, each (un)substituted C1-4 alkylcarbonyl or C1-6 alkyl; R11 = (un)substituted azolyl] are prepd. These compds. are useful for the treatment of tumor, diabetic retinopathy, chronic articular rheumatism, psoriasis, atherosclerosis , and Kaposi's sarcoma. They are also used for inhibiting neovascularization of a target blood vessel by contacting them with vascular endothelial cells of the target blood vessel. Thus, 100 mg 2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]aniline was dissolved in 5 mL CHCl3 and 0.5 mL Et3N, treated with a soln. of 100 mg triphosgene in CHCl3, and stirred at room temp. for 15 min, followed by adding 49 mg 2-aminothiazole, and the resulting mixt. was stirred at room temp. overnight to give 31 mg N-[2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl]-N;-(1,3-thiazol-2-yl)urea (II). II at 20 mg/kg/day for 9 days inhibited the growth of human lung cancer transplanted in nude mice by 92.0%. The compds. I in vitro showed IC50 of 0.001-0.0697 μM for inhibiting the phosphorylation of the intracellular domain of human vascular endothelial cell growth factor (VEGF) receptor KDR (kinase insert domain-contg. receptor) in IH3T3 cell expressing human KDR.

IT **475108-15-7P**, N-[3-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-N'-(3-isoxazolyl)urea
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-[(4-quinolinyl or 4-quinazolinyl)oxy]phenyl-N'-azolylurea derivs. as neovascularization inhibitors for treatment of tumor, diabetic retinopathy, chronic articular rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma)

RN 475108-15-7 HCAPLUS
CN Urea, N-[3-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-3-isoxazolyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:428885 HCAPLUS
DOCUMENT NUMBER: 137:6179
TITLE: Preparation of benzimidazoles as TIE-2 and/or VEGFR2 inhibitors
INVENTOR(S): Cheung, Mui; Harris, Philip Anthony; Hasegawa, Masaichi; Ida, Satoru; Kano, Kazuya; Nishigaki, Naohiko; Sato, Hideyuki; Veal, James Martin; Washio, Yoshiaki; West, Rob I.
PATENT ASSIGNEE(S): Glaxo Group Limited, UK; Glaxosmithkline K.K.
SOURCE: PCT Int. Appl., 217 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002044156	A2	20020606	WO 2001-US44553	20011128
WO 2002044156	A3	20021017		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002032439	A5	20020611	AU 2002-32439	20011128
EP 1341771	A2	20030910	EP 2001-991963	20011128

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.:	US 2000-253868P	P	20001129
	US 2001-310939P	P	20010808
	WO 2001-US44553	W	20011128

OTHER SOURCE(S): MARPAT 137:6179

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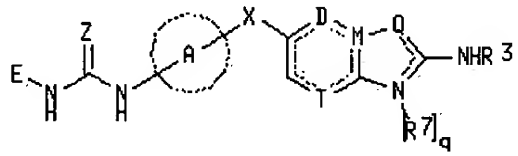

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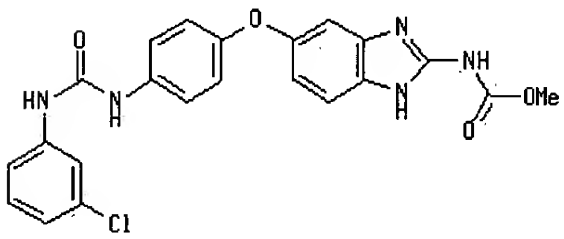


II

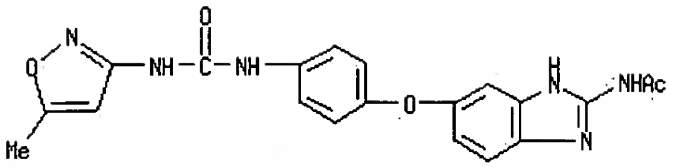
AB The title compds. [I; E = (un)substituted aryl, heteroaryl; A = aryl, heteroaryl, heterocyclyl; X = S, O, SO2, SO, CH2, CHOH, CO; Z = O, S; p = 0-1; q = 0-1; D = CH, T = CR8, M = C and Q = NT7p, wherein p = 0 and q = 1; or D = CH, T = CR8, M = C and Q = NR7p, wherein p =1 and q = 0, or D = CH, T = CR8, M = C and Q = S or O, wherein q = 0; or D = N, T = CR8, M = C and Q = NR7p, wherein either p or q = 0 and the other = 1; or D = CH, T = N, M = C and Q = NR7p, wherein either p or q = 0 and the other = 1; or D = CH, T = CR8, M = N and Q = CH, wherein q = 0; R1 = alkyl, haloalkyl, aryl, etc.; R2 = H, alkyl, aryl, etc.; R3 = alkylene or alkylene substituted by oxo, and is linked together with N atom to which it is attached and to one of the benzimidazole N atoms to form a heterocyclic compd. fused to the benzimidazole; R7 = H, alkyl, etc.; R8 = H, halo] and their salts, useful in the treatment of hyperproliferative diseases, were prepd. Thus, reacting Me [5-(4-aminophenoxy)-1H-benzimidazol-2-yl]carbamate (prepn. given) with 3-chlorophenyl isocyanate in THF afforded 69% II which showed pIC50 of > 7.0 in TIE-2 and VEGFR2 enzyme assays.

IT **433225-41-3P**

RL: CPN (Combinatorial preparation); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); CMBI (Combinatorial study); PREP (Preparation); USES (Uses)
(prepn. of benzimidazoles as TIE-2 and/or VEGFR2 inhibitors)

RN 433225-41-3 HCAPLUS

CN Acetamide, N-[5-[4-[[[(5-methyl-3-isoxazolyl)amino]carbonyl]amino]phenoxy]-1H-benzimidazol-2-yl]- (9CI) (CA INDEX NAME)



L9 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:314913 HCAPLUS
DOCUMENT NUMBER: 136:340689
TITLE: Preparation of urea derivatives containing nitrogenous aromatic ring compounds as inhibitors of angiogenesis
INVENTOR(S): Funahashi, Yasuhiro; Tsuruoka, Akihiko; Matsukura, Masayuki; Haneda, Toru; Fukuda, Yoshio; Kamata, Junichi; Takahashi, Keiko; Matsushima, Tomohiro; Miyazaki, Kazuki; Nomoto, Kenichi; Watanabe, Tatsuo; Obaishi, Hiroshi; Yamaguchi, Atsumi; Suzuki, Sachi; Nakamura, Katsuji; Mimura, Fusayo; Yamamoto, Yuji; Matsui, Junji; Matsui, Kenji; Yoshiba, Takako; Suzuki, Yasuyuki; Arimoto, Itaru
PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan
SOURCE: PCT Int. Appl., 699 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002032872	A1	20020425	WO 2001-JP9221	20011019
WO 2002032872	C1	20020926		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001095986	A5	20020429	AU 2001-95986	20011019
NO 2003001731	A	20030619	NO 2003-1731	20030414
US 2004053908	A1	20040318	US 2003-420466	20030418

PRIORITY APPLN. INFO.:

JP 2000-320420	A	20001020
JP 2000-386195	A	20001220
JP 2001-46685	A	20010222
WO 2001-JP9221	W	20011019

OTHER SOURCE(S): MARPAT 136:340689
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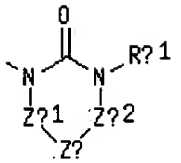
Q= 

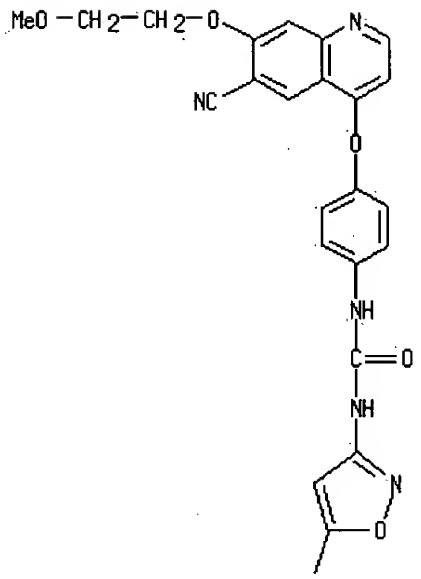
AB N-aryl or N-heteroarylurea derivs. represented by the general formula Ag-Xg-Yg-Tg1 or salts thereof, or hydrates of both [wherein Ag = (un)substituted C6-14 aryl or 5- to 14-membered heterocyclic group; Xg = single bond, O, S, C1-6 alkylene, SO, SO2, (un)substituted NH; Yg = (un)substituted C6-14 aryl, 5- to 14-membered heterocyclic group, C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl-C1-6 alkyl, 5- to 14-membered heteroaryl-C1-6 alkyl, (CH2)gSO2 (g = 1-8), (CH2)faCH:CH(CH2)fb (fa, fb = 0, 1,2,3), etc.; and Tg1 = a group of the general formula -Eg-CO-NRg1(Zg) or Q; wherein Eg = a single bond, (un)substituted NH; Rg1 = H, (un)substituted C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-8 aliph. hydrocarbyl, etc.; Zg = C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl, etc.; Zg1, Zg2 = (a) a single bond, (b) C1-6 alkylene optionally having ≥1 atoms selected from O, S, and N in the middle or the terminus of the chain and optionally substituted with oxo, (c) (un)substituted C2-6 alkenyl] are prepd. These compds. are also inhibitors of vascular endothelial growth factor receptor kinase (VEGFR2 kinase) and are useful as antitumor agents against hemangioma, pancreatic cancer, stomach cancer, colon cancer, breast cancer, prostate cancer, lung cancer, brain tumor, leukemia, or ovarian cancer, as cancer metastasis inhibitors, and for the treatment of retina neovascularization, diabetic retinopathy, atherosclerosis, or inflammatory diseases such as osteoarthritis, rheumatoid arthritis, psoriasis, or delayed hypersensitivity. Thus, to soln. of 334 mg 4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenylamine in 4 mL DMF were added 0.066 mL pyridine and 0.102 mL Ph chlorocarbonate and stirred at room temp. for 2.5 h to give 330 mg N-[4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea which (260 mg) was hydrogenolyzed over platinum oxide in ethanol overnight to give 160 mg N-[4-[6-(4-hydroxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea (I). I showed IC50 of 0.02 nM for inhibiting the vascular endothelial growth factor (VEGF)-stimulated sandwich tube formation in vascular endothelial cell.

IT **417714-38-6P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of urea derivs. contg. nitrogenous arom. ring compds. as angiogenesis inhibitors for prevention or treatment of diseases)

RN 417714-38-6 HCAPLUS

CN Urea, N-[4-[[6-cyano-7-(2-methoxyethoxy)-4-quinolinyl]oxy]phenyl]-N'-(5-methyl-3-isoxazolyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:325902 HCAPLUS
DOCUMENT NUMBER: 130:352546
TITLE: Preparation of amides containing leucine or methionine for inhibition of the interaction of vascular cell-adhesion molecule-1 (VCAM-1)and fibronectin with integrin very late antigen 4 (α4β1)
INVENTOR(S): Brittain, David Robert; Johnstone, Craig
PATENT ASSIGNEE(S): Zeneca Limited, UK
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9924398	A2	19990520	WO 1998-GB3334	19981109
WO 9924398	A3	19990805		

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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

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AU 9910420	A1	19990531	AU 1999-10420	19981109	
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EP 1030835	B1	20030122			
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JP 2001522831	T2	20011120	JP 2000-520412	19981109	
AT 231488	E	20030215	AT 1998-952872	19981109	
ZA 9810330	A	19990512	ZA 1998-10330	19981111	
NO 2000002158	A	20000711	NO 2000-2158	20000427	
US 6344570	B1	20020205	US 2000-554224	20000711	
PRIORITY APPLN. INFO.:			GB 1997-23789	A	19971112
			WO 1998-GB3334	W	19981109

OTHER SOURCE(S): MARPAT 130:352546
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

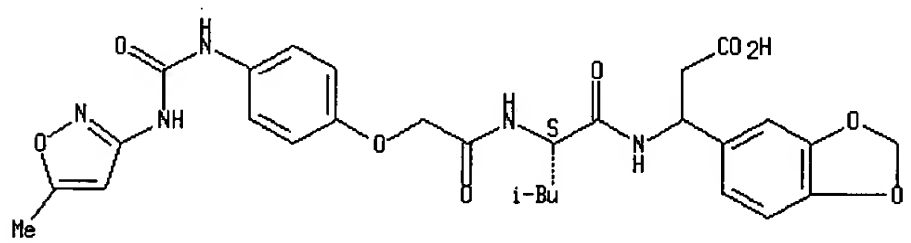
AB The title compds. [I; R1 = II (in the para or meta position); R2, R3 = H, NO2, alkyl, etc.; R2 and R3 together with the Ph to which they are attached form a 9-10 membered bicyclic ring system; R4 = alkyl; R5 = H, alkyl; R6 = alkyl, alkylcycloalkyl, alkylalkoxyl, etc.; R7 = alkyl, alkoxylcarbonyl, alkenyl, etc.; R8 = (un)substituted aryl, heteroaryl, bicyclic heteroaryl ring system linked to the nitrogen via a ring carbon, etc.; R9, R10 = H, alkyl; NR8R9 = dihydroindolyl, dihydroquinolinyl; R11 = CO2H, tetrazolyl, alkyl sulfonylcarbamyl, sulfo, sulfino; Y = O, S, SO2; m = 0-1; n = 0-4; with the proviso that when m and n cannot both be 0 and when m = 1, n = 0] and their pharmaceutically acceptable salts, useful in the treatment of multiple sclerosis, rheumatoid arthritis, asthma, coronary artery disease and psoriasis, were prepd. E.g., a multi-step synthesis of amide III was given. Compds. I are effective at 0.1-15 mg/kg/day.

IT **225101-10-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of amides contg. leucine or methionine for inhibition of the interaction of vascular cell-adhesion mol.-1 (VCAM-1)and fibronectin with integrin very late antigen 4 (α4β1))

RN 225101-10-0 HCAPLUS

CN β-Alanine, N-[[4-[[[(5-methyl-3-isoxazolyl)amino]carbonyl]amino]phenoxy]acetyl]-L-leucyl-3-(1,3-benzodioxol-5-yl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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FILE COVERS 1907-1966
FILE LAST UPDATED:  01 May 1997 (19970501/UP)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.  Title keywords, authors, patent
  assignees, and patent information, e.g., patent numbers, are
  now searchable from 1907-1966.  TIFF images of CA abstracts
  printed between 1907-1966 are available in the PAGE
  display formats.

  This file supports REG1stRY for direct browsing and searching of
  all substance data from the REGISTRY file.  Enter HELP FIRST for
  more information.

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     FILE 'REGISTRY' ENTERED AT 23:30:21 ON 29 MAR 2004
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L2           15 S L1
L3          238 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004
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L5            2 S L4 AND DUMAS, J?/AU
L6            9 S L4 NOT L5
L7            0 S L6 AND KHIRE, U?/AU
L8            1 S L6 AND LOWINGER, T?/AU
L9            8 S L6 NOT L8
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L11           0 S L9 AND RIEDL, B?/AU
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STRUCTURE FILE UPDATES: 28 MAR 2004 HIGHEST RN 668418-93-7
DICTIONARY FILE UPDATES: 28 MAR 2004 HIGHEST RN 668418-93-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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L22 STRUCTURE UPLOADED

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L22 HAS NO ANSWERS
L22 STR

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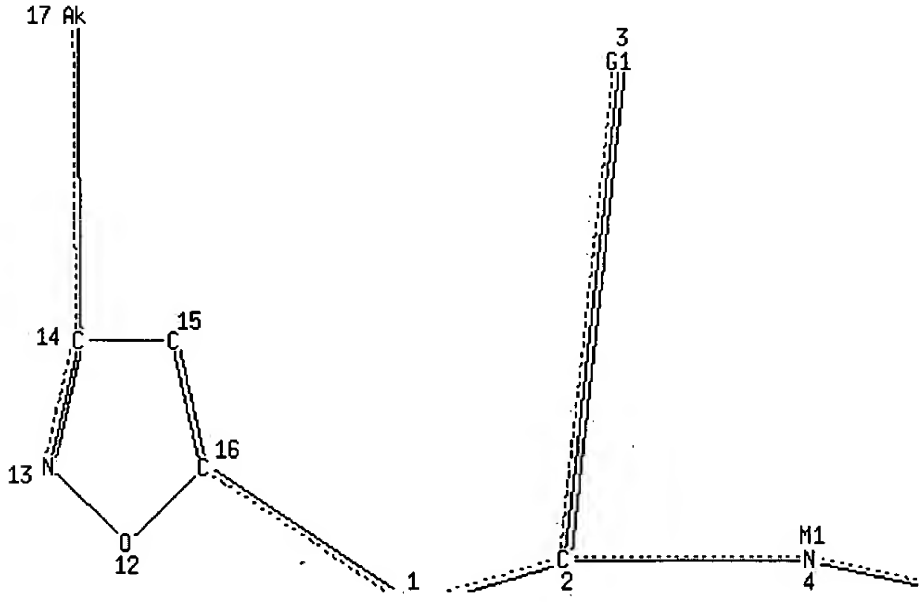
Page 1-D



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Page 1-F

Page 2-A

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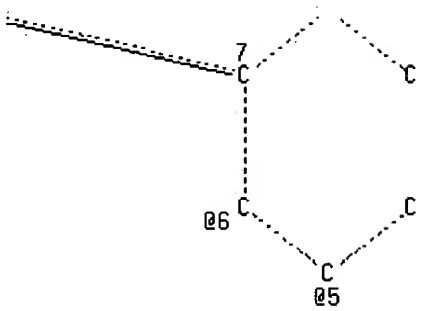
Page 2-B

Page 2-E



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STEREO ATTRIBUTES: NONE


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FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
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                                                     ENTRY    SESSION
FULL ESTIMATED COST                                 156.26     382.41

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)        SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                   0.00      -7.62

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FILE COVERS 1907 - 29 Mar 2004  VOL 140 ISS 14
FILE LAST UPDATED: 28 Mar 2004  (20040328/ED)

 This file contains CAS Registry Numbers for easy and accurate
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            665 DUMAS, J?/AU
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L26  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

ACCESSION NUMBER: 1999:425745 HCAPLUS
DOCUMENT NUMBER: 131:87909
TITLE: Inhibition of p38 kinase activity using substituted heterocyclic ureas
INVENTOR(S): **Dumas, Jacques**; Khire, Uday; Lowinger, Timothy Bruno; Paulsen, Holger; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Lee, Wendy; Redman, Aniko
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932111	A1	19990701	WO 1998-US26080	19981222
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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AU 9919971	A1	19990712	AU 1999-19971	19981222
AU 739642	B2	20011018		
EP 1041982	A1	20001011	EP 1998-964709	19981222
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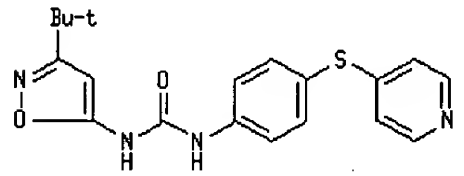
JP 2001526223	T2	20011218	JP 2000-525102	19981222
PRIORITY APPLN. INFO.:			US 1997-995750 A	19971222
			WO 1998-US26080 W	19981222

OTHER SOURCE(S): MARPAT 131:87909
GI



II

102 for Double Patenting

AB A method for treatment of p38-mediated disease other than cancer comprises

administration of ANHCONHB [I; A = substituted isoxazolyl, pyrazolyl, thienyl, furyl; B = (substituted) mono-, di-, or tricyclic aryl, heteroaryl contg. ≥1 5-6 membered arom. structure contg. 0-4 N, O, or S atoms]. Reaction of 4-(4-pyridinylthio)aniline with 3-tert-butyl-5-isoxazolyl isocyanate in toluene gave title compd. II. In an in vitro p38 kinase assay, I displayed IC50 values of 1-10 μM.

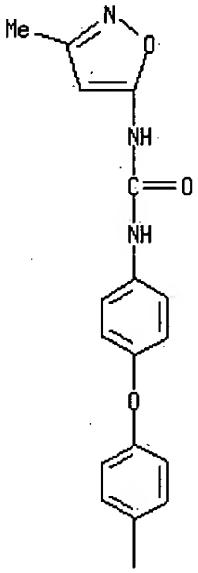
IT **229000-64-0P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of substituted heterocyclic ureas for treatment of p38 kinase-mediated diseases other than cancer)

RN 229000-64-0 HCAPLUS

CN Urea, N-(3-methyl-5-isoxazolyl)-N'-[4-(4-methylphenoxy)phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:425740 HCAPLUS
DOCUMENT NUMBER: 131:73648
TITLE: Inhibition of raf kinase using substituted heterocyclic ureas
INVENTOR(S): **Dumas, Jacques**; Khire, Uday; Lowinger, Timothy Bruno; Paulsen, Holger; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Lee, Wendy; Redman, Aniko
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 163 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932106	A1	19990701	WO 1998-US26078	19981222
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AU 9921989	A1	19990712	AU 1999-21989	19981222
EP 1047418	A1	20001102	EP 1998-965981	19981222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
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BR 9814374	A	20020514	BR 1998-14374	19981222
NO 2000003232	A	20000821	NO 2000-3232	20000621
BG 104597	A	20010228	BG 2000-104597	20000712

PRIORITY APPLN. INFO.: US 1997-996343 A 19971222
WO 1998-US26078 W 19981222

OTHER SOURCE(S): MARPAT 131:73648
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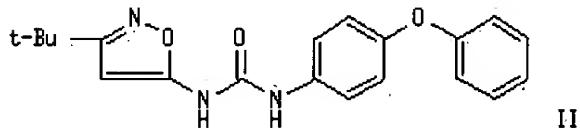


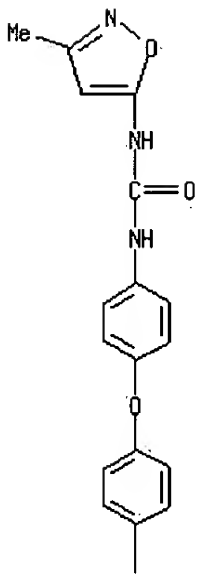
II

AB A method for treatment of cancerous cell growth mediated by raf kinase comprises administration of urea derivs. ANHCONHB [I; A = substituted isoxazolyl, thienyl, thiadiazolyl, furyl, pyrazolyl, etc.; B = (substituted) mono-, di-, or tricyclic aryl, heteroaryl contg. ≥1 5-6 membered arom. structure contg. 0-4 N, O, or S atoms]. Reaction of 4-phenyloxyphenyl isocyanate with 5-amino-3-tert-butylisoxazole in methylene chloride and heating at reflux temp. for 2 days gave title compd. II. In an in vitro raf kinase assay, I displayed IC50 values of 1-10 μM.

IT **229000-64-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of substituted heterocyclic ureas for treatment of cancerous cell growth mediated by raf kinase)

RN 229000-64-0 HCAPLUS
CN Urea, N-(3-methyl-5-isoxazolyl)-N'-[4-(4-methylphenoxy)phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L3 238 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004
L4 11 S L3
L5 2 S L4 AND DUMAS, J?/AU
L6 9 S L4 NOT L5
L7 0 S L6 AND KHIRE, U?/AU
L8 1 S L6 AND LOWINGER, T?/AU
L9 8 S L6 NOT L8
L10 0 S L9 AND PAULSEN, H?/AU
L11 0 S L9 AND RIEDL, B?/AU
L12 0 S L9 AND SCOTT, W?/AU
L13 0 S L9 AND SMITH, R?/AU
L14 0 S L9 AND WOOD, J?/AU
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L17 0 S L9 AND LEE, W?/AU
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L31           0 L27 AND RIEDL, B?/AU

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           189 SIBLEY, R?/AU
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L2           15 S L1
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L6            9 S L4 NOT L5
L7            0 S L6 AND KHIRE, U?/AU
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L9            8 S L6 NOT L8
L10           0 S L9 AND PAULSEN, H?/AU
L11           0 S L9 AND RIEDL, B?/AU
L12           0 S L9 AND SCOTT, W?/AU
L13           0 S L9 AND SMITH, R?/AU
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L15           0 S L9 AND HATOUM-MOKDAD, H?/AU
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L27 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

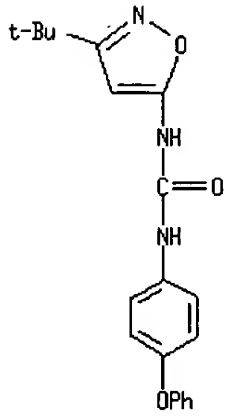
ACCESSION NUMBER: 2004:182368 HCAPLUS
TITLE: Three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands
INVENTOR(S): Come, Jon H.; Becker, Frank; Kley, Nikolai A.; Reichel, Christoph
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 238 pp., Cont.-in-part of U.S. Ser. No. 91,177.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004043388	A1	20040304	US 2002-234985	20020903
US 2003165873	A1	20030904	US 2002-91177	20020304

PRIORITY APPLN. INFO.:

US 2001-272932P	P	20010302
US 2001-278233P	P	20010323
US 2001-329437P	P	20011015
US 2002-91177	A2	20020304

AB The invention provides compns. and methods for isolating ligand-binding polypeptides for a user-specified ligand, and for isolating small mol. ligands for a user-specified target polypeptide using an improved class of hybrid ligand compds. Prepn. of compds., e.g a methotrexate moiety linked by a polyethylene gycol moiety to dexamethasone, is described.
IT INDEXING IN PROGRESS
IT 229000-80-0D, conjugates
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands)
RN 229000-80-0 HCAPLUS
CN Urea, N-[3-(1,1-dimethylethyl)-5-isoxazolyl]-N'-(4-phenoxyphenyl)- (9CI) (CA INDEX NAME)



L27 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:892762 HCAPLUS
DOCUMENT NUMBER: 139:395938
TITLE: Preparation of ureas as positive allosteric modulators of the nicotinic acetylcholine receptor
INVENTOR(S): Piotrowski, David W.; Rogers, Bruce N.; McWhorter, William W., Jr.; Walker, Daniel P.; Corbett, Jeffrey W.; Groppi, Vincent E., Jr.; Rudmann, Daniel G.
PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA
SOURCE: PCT Int. Appl., 159 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

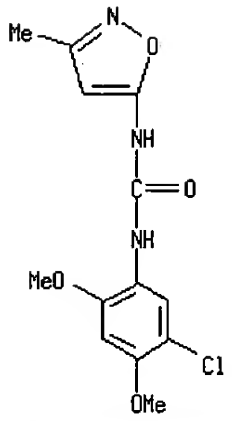
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003093250	A2	20031113	WO 2003-US11493	20030428
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003236287	A1	20031225	US 2003-423062	20030425
PRIORITY APPLN. INFO.:			US 2002-377364P P	20020503
			US 2003-456941P P	20030324

OTHER SOURCE(S): MARPAT 139:395938

AB ANHCXNHB [X = O, S; A = (un)substituted Ph, 6-membered N heteroaryl; B = (un)substituted 5-6-membered heteroaryl] were prepd. to treat diseases or conditions in which the α7 nAChR is known to be involved (no data). Thus, 2,4-Me(MeO)C6H3NH2 was treated with 3-F3CC6H4CNO to give 2,4-Me(MeO)C6H3NHCONHC6H4CF3-3.

IT **625117-71-7P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of ureas as pos. allosteric modulators of the nicotinic acetylcholine receptor)

RN 625117-71-7 HCAPLUS
CN Urea, N-(5-chloro-2,4-dimethoxyphenyl)-N'-(3-methyl-5-isoxazolyl)- (9CI) (CA INDEX NAME)



L27 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:849617 HCAPLUS
DOCUMENT NUMBER: 137:370101
TITLE: Preparation of quinoline derivatives having azolyl group and quinazoline derivatives as antitumor agents
INVENTOR(S): Kubo, Kazuo; Sakai, Teruyuki; Nagao, Rika; Fujiwara, Yasunari; Isoe, Toshiyuki; Hasegawa, Kazumasa
PATENT ASSIGNEE(S): Kirin Beer Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002088110	A1	20021107	WO 2002-JP4279	20020426
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JP 2003012668	A2	20030115	JP 2002-126869	20020426
US 2003087907	A1	20030508	US 2002-132473	20020426
EP 1382604	A1	20040121	EP 2002-724651	20020426
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NO 2003004595	A	20031219	NO 2003-4595	20031014

PRIORITY APPLN. INFO.: JP 2001-132775 A 20010427
WO 2002-JP4279 W 20020426

OTHER SOURCE(S): MARPAT 137:370101
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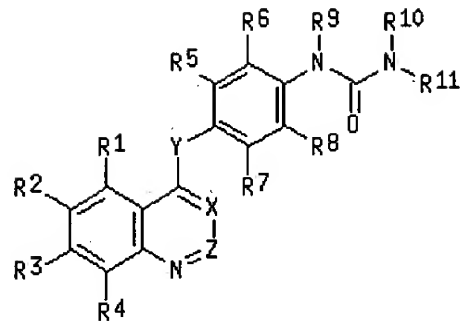


I

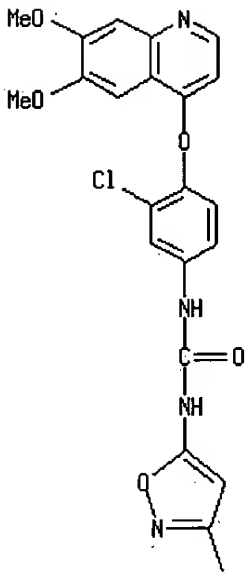
AB N-[(4-quinolinyl or 4-quinazolinyl)thio or -oxy]phenyl-N'-azolylurea derivs. represented by the formula (I) or pharmaceutically acceptable salts or solvates thereof [wherein X, Z = CH, N; Y = O, S; R1, R2, R3 = H, NO2, NH2, each (un)substituted C1-6 alkyl or alkoxy or C2-6 alkenyl or alkynyl; R4 = H; R5-R8 = H, halo, C1-4 alkyl, alkoxy, or alkylthio, CF3, NO2, NH2; R9, R10 = C1-6 alkyl, each (un)substituted C1-4 alkylcarbonyl or C1-6 alkyl; R11 = (un)substituted azolyl] are prepd. These compds. are useful for the treatment of tumor, diabetic retinopathy, chronic articular rheumatism, psoriasis, atherosclerosis , and Kaposi's sarcoma. They are also used for inhibiting neovascularization of a target blood vessel by contacting them with vascular endothelial cells of the target blood vessel. Thus, 100 mg 2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]aniline was dissolved in 5 mL CHCl3 and 0.5 mL Et3N, treated with a soln. of 100 mg triphosgene in CHCl3, and stirred at room temp. for 15 min, followed by adding 49 mg 2-aminothiazole, and the resulting mixt. was stirred at room temp. overnight to give 31 mg N-[2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl]-N;-(1,3-thiazol-2-yl)urea (II). II at 20 mg/kg/day for 9 days inhibited the growth of human lung cancer transplanted in nude mice by 92.0%. The compds. I in vitro showed IC50 of 0.001-0.0697 μM for inhibiting the phosphorylation of the intracellular domain of human vascular endothelial cell growth factor (VEGF) receptor KDR (kinase insert domain-contg. receptor) in IH3T3 cell expressing human KDR.

IT **475108-16-8P**, N-[3-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-N'-(3-methyl-5-isoxazolyl)urea
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-[(4-quinolinyl or 4-quinazolinyl)oxy]phenyl-N'-azolylurea derivs. as neovascularization inhibitors for treatment of tumor, diabetic retinopathy, chronic articular rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma)

RN 475108-16-8 HCAPLUS

CN Urea, N-[3-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(3-methyl-5-isoxazolyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



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REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:314913 HCAPLUS
DOCUMENT NUMBER: 136:340689
TITLE: Preparation of urea derivatives containing nitrogenous aromatic ring compounds as inhibitors of angiogenesis
INVENTOR(S): Funahashi, Yasuhiro; Tsuruoka, Akihiko; Matsukura, Masayuki; Haneda, Toru; Fukuda, Yoshio; Kamata, Junichi; Takahashi, Keiko; Matsushima, Tomohiro; Miyazaki, Kazuki; Nomoto, Kenichi; Watanabe, Tatsuo; Obaishi, Hiroshi; Yamaguchi, Atsumi; Suzuki, Sachi; Nakamura, Katsuji; Mimura, Fusayo; Yamamoto, Yuji; Matsui, Junji; Matsui, Kenji; Yoshiba, Takako; Suzuki, Yasuyuki; Arimoto, Itaru
PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan
SOURCE: PCT Int. Appl., 699 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002032872	A1	20020425	WO 2001-JP9221	20011019
WO 2002032872	C1	20020926		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
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BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001095986	A5	20020429	AU 2001-95986	20011019
NO 2003001731	A	20030619	NO 2003-1731	20030414
US 2004053908	A1	20040318	US 2003-420466	20030418

PRIORITY APPLN. INFO.:

JP 2000-320420	A	20001020
JP 2000-386195	A	20001220
JP 2001-46685	A	20010222
WO 2001-JP9221	W	20011019

OTHER SOURCE(S): MARPAT 136:340689
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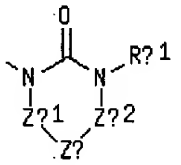
Q= 

AB N-aryl or N-heteroarylurea derivs. represented by the general formula Ag-Xg-Yg-Tg1 or salts thereof, or hydrates of both [wherein Ag = (un)substituted C6-14 aryl or 5- to 14-membered heterocyclic group; Xg = single bond, O, S, C1-6 alkylene, SO, SO2, (un)substituted NH; Yg = (un)substituted C6-14 aryl, 5- to 14-membered heterocyclic group, C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl-C1-6 alkyl, 5- to 14-membered heteroaryl-C1-6 alkyl, (CH2)gSO2 (g = 1-8), (CH2)faCH:CH(CH2)fb (fa, fb = 0, 1,2,3), etc.; and Tg1 = a group of the general formula -Eg-CO-NRg1(Zg) or Q; wherein Eg = a single bond, (un)substituted NH; Rg1 = H, (un)substituted C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-8 aliph. hydrocarbyl, etc.; Zg = C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl, etc.; Zg1, Zg2 = (a) a single bond, (b) C1-6 alkylene optionally having ≥1 atoms selected from O, S, and N in the middle or the terminus of the chain and optionally substituted with oxo, (c) (un)substituted C2-6 alkenyl] are prepd. These compds. are also inhibitors of vascular endothelial growth factor receptor kinase (VEGFR2 kinase) and are useful as antitumor agents against hemangioma, pancreatic cancer, stomach cancer, colon cancer, breast cancer, prostate cancer, lung cancer, brain tumor, leukemia, or ovarian cancer, as cancer metastasis inhibitors, and for the treatment of retina neovascularization, diabetic retinopathy, atherosclerosis, or inflammatory diseases such as osteoarthritis, rheumatoid arthritis, psoriasis, or delayed hypersensitivity. Thus, to soln. of 334 mg 4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenylamine in 4 mL DMF were added 0.066 mL pyridine and 0.102 mL Ph chlorocarbonate and stirred at room temp. for 2.5 h to give 330 mg N-[4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea which (260 mg) was hydrogenolyzed over platinum oxide in ethanol overnight to give 160 mg N-[4-[6-(4-hydroxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea (I). I showed IC50 of 0.02 nM for inhibiting the vascular endothelial growth factor (VEGF)-stimulated sandwich tube formation in vascular endothelial cell.

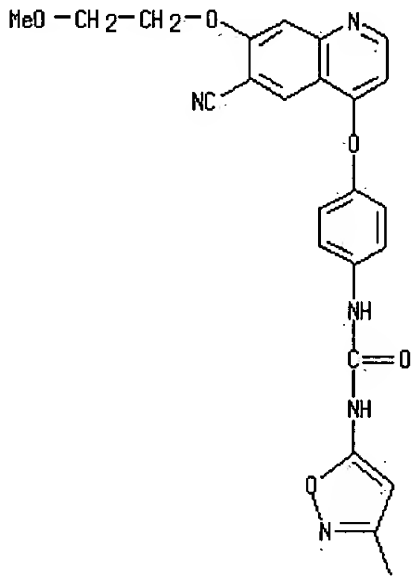
IT **417714-37-5P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of urea derivs. contg. nitrogenous arom. ring compds. as angiogenesis inhibitors for prevention or treatment of diseases)

RN 417714-37-5 HCAPLUS

CN Urea, N-[4-[[6-cyano-7-(2-methoxyethoxy)-4-quinolinyl]oxy]phenyl]-N'-(3-methyl-5-isoxazolyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1959:34516 HCAPLUS
DOCUMENT NUMBER: 53:34516
ORIGINAL REFERENCE NO.: 53:6122h-i,6123a
TITLE: Synthesis of several asymmetrically substituted derivatives of thiourea with potential tuberculostatic activity
AUTHOR(S): Oeriv, S.; Voinescu, M.; Wexler, B.; Gloter, E.
SOURCE: Acad. rep. populare Romine, Studii cercetari chim. (1958), 6, 155-60
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

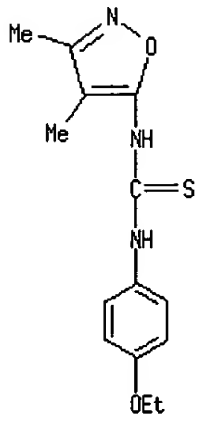
AB The following p-ROC6H4NHCSCH2CH:CH2 (R and m.p. given) were prepd. from CH2:CHCH2NCS and the corresponding p-ROC6H4NH2: Me, 78°; Et, 97°; CH2:CHCH2, 74°; Pr, 68°; Me2CHCH2, 105-6°; Bu, 84-5°; n-C8H17, 86-7°. Their tuberculostatic activity in vitro varied from a diln. of 1/180,000 to 1/1,800,000. N-(p-Ethoxyphenyl)-N'-(3,4-dimethyl-5-isoxazolyl)isothiourea, m. 171-2°, prepd. from p-EtOC6H4NCS and

3,4-dimethyl-5-aminoisoxazole, had an activity in vitro at a diln. of 1/10,000,000.

IT 100720-16-9, Urea, 1-(3,4-dimethyl-5-isoxazolyl)-3-(p-ethoxyphenyl)-2-thio-
(prepn. of)

RN 100720-16-9 HCAPLUS

CN Urea, 1-(3,4-dimethyl-5-isoxazolyl)-3-(p-ethoxyphenyl)-2-thio- (6CI) (CA INDEX NAME)



=> d his

(FILE 'HOME' ENTERED AT 23:30:16 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 23:30:21 ON 29 MAR 2004

L1 STRUCTURE UPLOADED
L2 15 S L1
L3 238 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004

L4 11 S L3
L5 2 S L4 AND DUMAS, J?/AU
L6 9 S L4 NOT L5
L7 0 S L6 AND KHIRE, U?/AU
L8 1 S L6 AND LOWINGER, T?/AU
L9 8 S L6 NOT L8
L10 0 S L9 AND PAULSEN, H?/AU
L11 0 S L9 AND RIEDL, B?/AU
L12 0 S L9 AND SCOTT, W?/AU
L13 0 S L9 AND SMITH, R?/AU
L14 0 S L9 AND WOOD, J?/AU
L15 0 S L9 AND HATOUM-MOKDAD, H?/AU
L16 0 S L9 AND JOHNSON, W?/AU
L17 0 S L9 AND LEE, W?/AU
L18 0 S L9 AND REDMAN, A?/AU
L19 0 S L9 AND SIBLEY, R?/AU
L20 0 S L9 AND RENICK, J?/AU

FILE 'CAOLD' ENTERED AT 23:36:53 ON 29 MAR 2004

L21 0 S L3

FILE 'REGISTRY' ENTERED AT 23:37:00 ON 29 MAR 2004

L22 STRUCTURE UPLOADED
L23 4 S L22

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L24          110 S L22 FULL

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L25            7 S L24
L26            2 S L25 AND DUMAS, J?/AU
L27            5 S L25 NOT L26
L28            0 S L27 AND KHIRE, U?/AU
L29            0 S L27 AND LOWINGER, T?/AU
L30            0 S L27 AND PAULSEN, H?/AU
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L32            0 S L27 AND SCOTT, W?/AU
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L34            0 S L27 AND WOOD, J?/AU
L35            0 S L27 AND HATOUM-MOKDAD, H?/AU
L36            0 S L27 AND JOHNSON, J?/AU
L37            0 S L27 AND LEE, W?/AU
L38            0 S L27 AND REDMAN, A?/AU
L39            0 S L27 AND SIBLEY, R?/AU
L40            0 S L27 AND RENICK, J?/AU

=> s l24
L41            7 L24

=> file caold
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FULL ESTIMATED COST                               45.09     427.50

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)    SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                               -4.85     -12.47

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FILE COVERS 1907-1966
FILE LAST UPDATED:  01 May 1997 (19970501/UP)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.  Title keywords, authors, patent
  assignees, and patent information, e.g., patent numbers, are
  now searchable from 1907-1966.  TIFF images of CA abstracts
  printed between 1907-1966 are available in the PAGE
  display formats.

  This file supports REG1stRY for direct browsing and searching of
  all substance data from the REGISTRY file.  Enter HELP FIRST for
  more information.

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L1                STRUCTURE UPLOADED
L2             15 S L1
L3            238 S L1 FULL
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     FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004
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L5             2 S L4 AND DUMAS, J?/AU
L6             9 S L4 NOT L5
L7             0 S L6 AND KHIRE, U?/AU
L8             1 S L6 AND LOWINGER, T?/AU
L9             8 S L6 NOT L8
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L21            0 S L3

     FILE 'REGISTRY' ENTERED AT 23:37:00 ON 29 MAR 2004
L22              STRUCTURE UPLOADED
L23            4 S L22
L24          110 S L22 FULL

     FILE 'HCAPLUS' ENTERED AT 23:38:41 ON 29 MAR 2004
L25            7 S L24
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L40            0 S L27 AND RENICK, J?/AU
L41            7 S L24

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=> s 124
L42            1 L24

=> d 142, all, 1

L42  ANSWER 1 OF 1  CAOLD  COPYRIGHT 2004 ACS on STN
AN   CA53:6122i  CAOLD
TI   synthesis of asym. substituted derivs. of thiourea with potential
     tuberculostatic activity
AU   Oeriu, Simion; Voinescu, M.; Wexler, B.; Gloter, E.
IT   1138-72-3   1142-30-9 100615-38-1 100720-16-9 100875-53-4 100875-54-5
     101264-75-9 101872-56-4
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ANSWER 1  REGISTRY  COPYRIGHT 2004 ACS on STN
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CN   Urea, 1-(3,4-dimethyl-5-isoxazolyl)-3-(p-ethoxyphenyl)-2-thio- (6CI)  (CA
     INDEX NAME)
FS   3D CONCORD
MF   C14 H17 N3 O2 S
SR   CAOLD
LC   STN Files:   BEILSTEIN*, CA, CAOLD, CAPLUS
         (*File contains numerically searchable property data)
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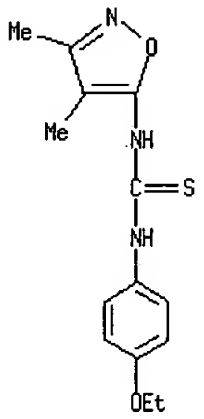


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

               1 REFERENCES IN FILE CA (1907 TO DATE)
               1 REFERENCES IN FILE CAPLUS (1907 TO DATE)
               1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)



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                                                       ENTRY    SESSION
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STN INTERNATIONAL LOGOFF AT 23:42:03 ON 29 MAR 2004
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